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ORIGINAL RESEARCH ARTICLE

Evaluation of preventive effect of quercetin on doxorubicin-induced nephrotoxic rat model by [^{99m}Tc]Tc-DMSA renal cortical scintigraphy and biochemical methods

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ABSTRACT

Introduction: The purpose of this study was to evaluate possible preventive role of quercetin on doxorubicin (DOX) induced kidney toxicity using Tc-99m Dimercaptosuccinic Acid ([^{99m}Tc]Tc-DMSA) renal cortical scintigraphy and biochemical approaches.

Methods: 28 Male wistar rats were separated into four groups. First group was intraperitoneally (i.p.) injected saline and regarded as the control group; second one was received 18 mg/kg/i.p doxorubicin for three days at a 24 h interval; the third and last group received 10 mg/kg and 100 mg/kg quercetin for 21 days and for the last 3 days doxorubicin and quercetin were administrated together at the same time. On the 22nd day of the experiment, [^{99m}Tc]Tc-DMSA renal cortical scintigraphy and biochemical parameters were measured.

Results: DOX administration significantly increased blood urea nitrogen (845%) and creatinine (702%) levels in serum; nitric oxide (158%), plasma tumor necrosis factor-alpha (233%) and interleukin-6 (191%) levels in kidney tissue, and also reduced [^{99m}Tc]Tc-DMSA uptake by 29% in the kidneys as well. Pre-treatment with quercetin mitigated such alterations in all mentioned parameters.

Conclusion: All data indicate that oxidative stress and inflammatory processes are involved in DOX-induced nephrotoxicity, which might be decreased by quercetin. In addition, [^{99m}Tc]Tc-DMSA scintigraphic may be a good method for demonstrating doxorobucin-induced renal injury.

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INTRODUCTION

Doxorubicin (DOX) is an anti-cancer drug being a member of the anthracycline antibiotic group. It has been used successfully in the treatment of various cancer conditions such as lymphoma, leukemia as well as solid tumors for a long time [1, 2].

Kidneys seem to be one of the most susceptible organs that may be exposed to the drug's side effects owing to their high blood perfusion rate, expression functions, and metabolic activity [3]. In animal models of DOX-induced nephrotoxicity; tubular necrosis, tubular dilatation, glomerular vacuolization, increased glomerular permeability, and glomerular atrophic appearance have been demonstrated. [4]. A lot of researcher suggested that inflammation and oxidative stress play key role in the pathogenesis of DOX-induced renal toxicity [5-8]. DOX induces the formation of free radical and pro-inflammatory cytokines, increases the lipid peroxidation, causes the functional and structural change of the cells, and eventually leads to renal cell death [9-11].

Recently, the accepted opinion is that the addition of antioxidant to treatment may alleviate DOX induced toxicity [10, 12, 13]. Quercetin is the most abundant flavonoid in Mediterranean type nutrition. Quercetin fights against oxidative stress by inhibiting oxidation molecules and free radicals [14-17]. Moreover, quercetin effectively blocks the inflammatory processes in cell [17,18]. All these antioxidant and cytoprotective effect of quercetin may exhibits a potential antitoxic effect in cell.

[^{99m}Tc]Tc-DMSA is a radiopharmaceutical that allows visualizing the renal cortex by a rate of 40-65% bind to proximal tubular cells in the renal cortex at 2 hours after injection. Renal cortical scintigraphy with [^{99m}Tc]Tc-DMSA is a non-invasive functional imaging technique that is frequently used to detect cortical defects of acute pyelonephritis and scar formation associated with chronic pyelonephritis [19]. In preclinical studies, nephrotoxicity caused by chemotherapy agents has been shown to detect deterioration of renal function by [^{99m}Tc]Tc-DMSA scintigraphy even when no pathological findings are detected in laboratory measurements [20].

The purpose of the present study was to demonstrate the renoprotective effect of quercetin in the prevention of DOX nephrotoxicity detected by scintigraphic and biochemical methods.

METHODS

Animals

Twenty-eight adult male Wistar Albino rats [n: 28; 12 weeks old; weight: 220-280 g] were used in this experimental study. Rats were purchased from the Experimental Animal Center of Tokat Gaziosmanpaşa University [Tokat/Turkey]. Ethical approval was obtained from Tokat Gaziosmanpasa University Local Ethics Committee for Animal Experiments [approval number: 2019 HADYEK-27]. The rats were maintained in a laboratory room with a 12:12 h dark: light cycle, at a temperature of 23˚C, 50% humidity. The rat had access to commercial food pellets and water ad libitum.

Chemicals

Quercetin was obtained from Sigma-Aldrich. DOX was obtained from local pharmacology.

Experimental strategy

The rats were randomly divided into four groups, each containing seven rats:

Group I: Control, serum physiologic [4 ml/kg] administered intraperitoneally [i.p] every day for 21 day, [CON].

Group II: Doxorubicin group [DOX 18 mg/kg/i.p], [DOX].

Group III: Quercetin 10 mg/kg injection followed by DOX 18 mg/kg injection, [QRC10+DOX] group.

Group IV: Quercetin 100 mg/kg injection followed by DOX 18 mg/kg injection, [QRC100+DOX] group.

Quercetin was dissolved in serum physiologic and administered intraperitoneally every day for 21 day, at doses of 10 or 100 mg/kg/body weight. DOX was injected the rat following quercetin pretreatment. DOX was dissolved in serum physiologic and administered intraperitoneally a total cumulative dose of 18 mg/kg, at an interval of 24 h, for three day in study [19th, 20th, and 21st].

Scintigraphic imaging with [^{99m}Tc]Tc-DMSA

Renal scintigraphy was performed two hours after injection of 1 mCi/kg (37 MBq) of [^{99m}Tc]Tc-DMSA through the tail vein using a dual head gamma camera detector with a low-energy collimator for the acquisition of layered static images over a 10-min period with a matrix of 64 × 64 pixels and 140 keV ± 20% energy window [E-CAM, Siemens, Germany]. Regions of interest [ROIs] were selected around the kidneys and background areas for both anterior and posterior images. For semiquantitative analyses, ROIs were drawn around each kidney. DMSA uptake was expressed by subtracting the

background level. After background correction, the geometric mean of the anterior and posterior images was used for the calculation of left and right renal [^{99m}Tc]Tc-DMSA uptake. Semi-quantitative [^{99m}Tc]Tc-DMSA uptake was determined for each kidney by calculating the radioactivity count per minute (cpm). The sum of the [^{99m}Tc]Tc-DMSA uptake values of the right and left kidneys was obtained for each rat.

Measurement of blood parameters [BUN and creatinine]

On the 22nd day of the experiment, after scintigraphic evaluation, blood samples were taken from the heart hearth and collected in the EDTA tubes. The EDTA tubes were centrifuged at 3.000 rpm for 5 min. The levels of BUN and creatinine were studied from the serum samples with enzyme linked immunosorbent assays [ELISA] method.

Measurement of kidney tissue parameters [TNF-α, IL-6 and NO]

All kidney tissue samples were washed out with the cold isotonic saline solution (0.9%) and wet tissue weights were weighed. Then, kidney tissue was cut into small pieces with scalpel and homogenized in the cold PBS (pH 7.4). The kidney tissues for the supernatant were centrifuged at 2500 rpm for 20 min. TNF-α, IL-6 and NO parameters were examined with the quantitative sandwich enzyme immunoassay (ELISA) kits (Bioassay Technology Laboratory). TNF-α (Rat Tumor Necrosis Factor Alpha ELISA), IL-6 (Rat Interleukin 6 ELISA) and NO (Rat Nitric Oxide ELISA) kits were used.

Statistical analysis

One-way analysis of variance (ANOVA) followed by a multiple comparisons Tukey's test was used for statistical comparisons. All statistical tests were performed using the Statistical Package for Social Sciences (SPSS) 20.0 software (SPSS, Inc., Chicago, IL, USA). All parameters are presented as the mean ± SEM (standard error of the mean). P<0.05 values were considered to indicate a statistically important.

RESULTS

Analysis of scintigraphic parameters in [^{99m}Tc]Tc-DMSA

Our results showed that rat kidneys presented some alterations in the scintigraphic imaging. As shown in Figure 1, significantly decreased the [^{99m}Tc]Tc-DMSA uptake levels in the kidneys were seen in DOX, QRC10+DOX and QRC100+DOX groups when compared to the CON group. However, significantly increased [^{99m}Tc]Tc-DMSA uptake levels in the kidney were detected in the QRC10+DOX and QRC100+DOX groups (p<0.001); when compared to the DOX group. In addition, QRC100+DOX groups exhibited enhanced [^{99m}Tc]Tc-DMSA levels in the kidneys (p<0.01) compared to the QRC10+DOX group (Figure 1).

Analysis of blood parameters (BUN and creatinine)

As shown in Figure 2, creatinine and BUN parameters were significantly increased in DOX, QRC10+DOX or QRC100+DOX groups compared to CON group (p<0.001). However, QRC10+DOX or QRC100+DOX group significantly reduced BUN (p<0.01; p<0.001, respectively) and creatinine parameters (p<0.001; p<0.001, respectively) when compared to DOX group. QRC100+DOX group exhibited significantly reduced BUN levels when compared to QRC10+DOX group (p<0.001), but creatinine parameters did not alter (P >0.05), (Figure 2).

Analysis of kidney tissue parameters [TNF-α, IL-6 and NO]

Figure 3 illustrates the analysis of IL-6, TNF-α, and NO parameters in the kidney tissue. The TNF-α and IL-6 parameters were significantly increased in the DOX (p<0.001), QRC10+DOX (p<0.001), QRC100+DOX (p<0.001; p<0.05, respectively) groups compared with CON group. Furthermore, DOX, QRC10+DOX group exhibited a higher level of NO compared with the CON group (p<0.001; p<0.05, respectively), but statistical significance alteration did not observed at NO levels in QRC100+DOX group compared to CON group (p >0.05). QRC10+DOX and QRC100+DOX groups exhibited significantly reduced TNF-α (QRC10; p<0.05; and QRC100; p<0.001) and NO parameters in kidney tissue (QRC10; p<0.05 and QRC100; p<0.01) compared with DOX group. In addition, IL-6 levels were significantly decreased at QRC100+DOX group (p<0.01); yet, no statistical significance was measured between QRC10+DOX group and DOX group (p>0.05). Significantly reduced TNF-α, IL-6 and NO levels were detected in QRC100+DOX group compared to QRC10+DOX group (p<0.001; p<0.001; p<0.05 respectively).

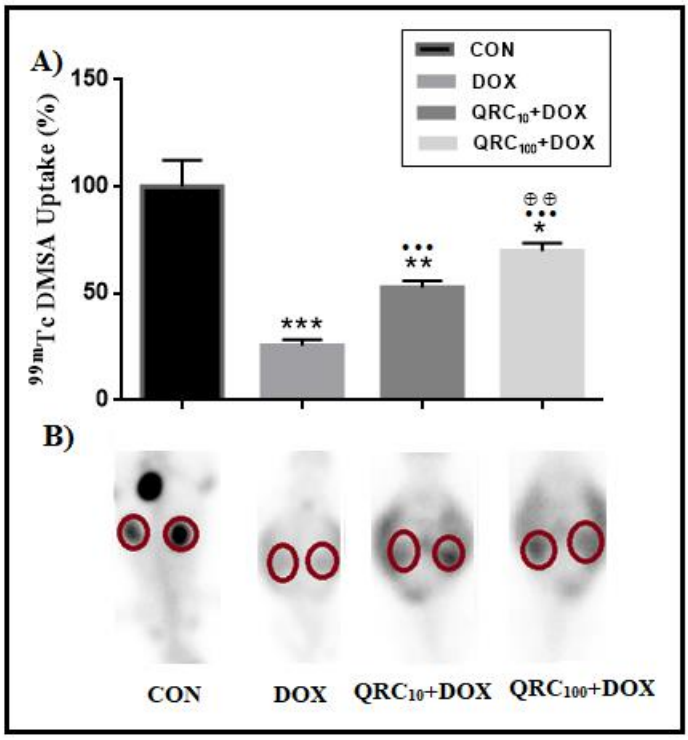

Fig 1. A) Changes in kidney [^{99m}Tc]Tc-DMSA uptake level in all groups. B) Kidney scintigraphy images of the rats. The [^{99m}Tc]Tc-DMSA uptake (cpm) level reduced in both kidneys of the animal in DOX group. Decrease in ^{99m}Tc-DMSA uptake level indicates renal damage. [^{99m}Tc]Tc-DMSA uptake level increased in and QRC10+DOX and QRC100+DOX group.
*p<0.05; **p<0.01;*** p<0.001; significant difference compared to CON groups
●●● p<0.001 for the DOX group compared to with the QRC10+DOX or QRC100+DOX group
⊕⊕ p<0.01 for the QRC10+DOX group when compared to with the QRC100+DOX group
(Control [CON], doxorubicin [DOX], quercetin [QRC])

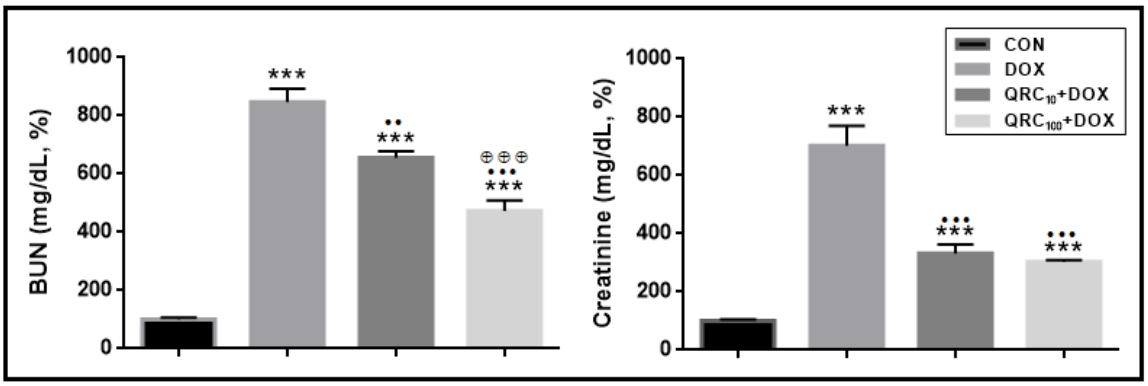

Fig 2. Changes in biochemical BUN (left) and creatinine (right) parameters in all groups.
***: p<0.001, important difference compared to CON groups
●● p<0.01; ●●● p<0.001 for the DOX group compared to with the QRC10+DOX or QRC100+DOX groups
⊕⊕⊕ : p<0.001, for the QRC10+DOX group compared to with the QRC100+DOX group
(Control [CON], doxorubicin [DOX], quercetin [QRC])

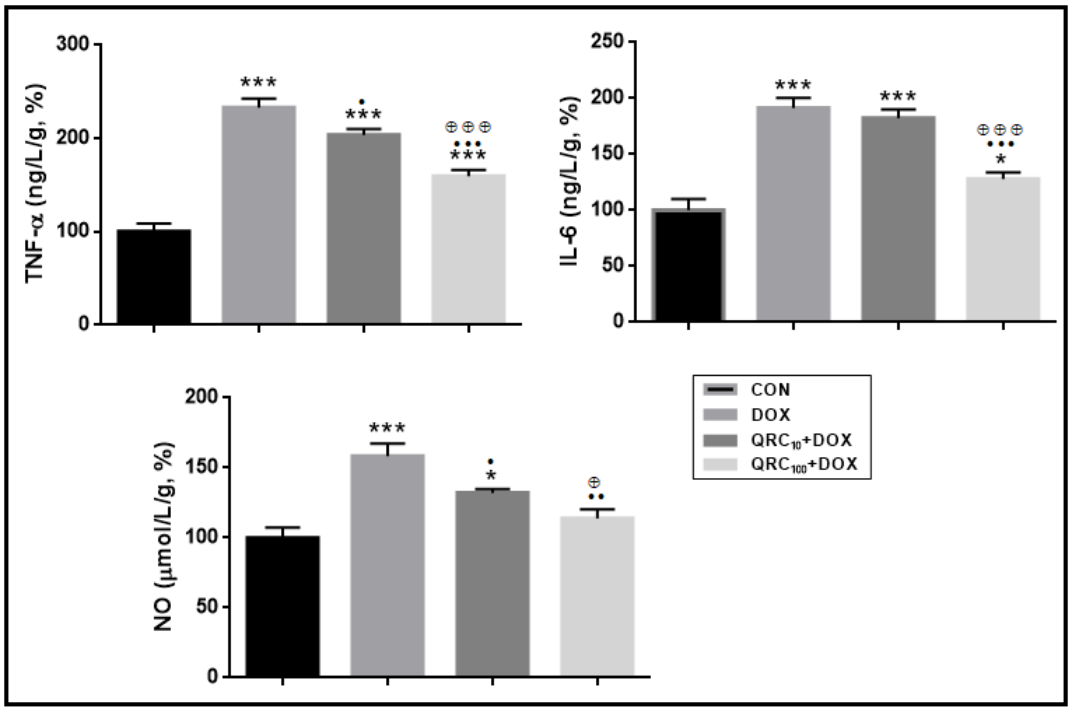

Fig 3. Changes in kidney tissue of TNF-α, IL-6, NO in all groups.
*: p<0.05, ***: p<0.001, significant difference compared to CON groups
• p<0.05; ••• p<0.001 for the DOX group compared to with the QRC10+DOX or QRC100+DOX groups
⊕ p<0.05; ⊕⊕⊕ : p<0.001, for the QRC10+DOX group compared to with the QRC100+DOX group
(Control [CON], doxorubicin [DOX], quercetin [QRC])

DISCUSSION

In the current study, we investigated possible protective effects of 10 and 100 mg/kg quercetin treatment against DOX-induced nephrotoxicity. The results showed that DOX administration increased BUN and creatinine levels in serum, and TNF-alpha, IL-6 and NO in kidney tissue. In addition, reduced [^{99m}Tc]Tc-DMSA uptake level was observed at this group's kidney. All these effects were attenuated by treatment with 10 and 100 mg/kg quercetin.

DOX is a first-line antineoplastic drug used for many cancer treatments. However, its clinical use is limited due to its serious side effects to the many organs including kidneys. A lot of studies indicated that various mechanisms including inflammation and oxidative stress have been an important role in the induction of the renal toxicity associated with the DOX [5, 8, 21]. It is stated that a key mechanism in the DOX-induced nephrotoxicity is oxidative stress [5]. Previous studies demonstrated that DOX administration induces reactive oxygen species (ROS) generation including NO, as well as increases in inflammatory cytokines including IL-6 and TNF-a, lead to oxidative stress and inflammation in cell [6, 9, 22]. In addition, TNF-α induces NO synthase formation and therefore further increases oxidative stress [6, 8, 23]. Our results showed that NO, TNF-a and IL-6 levels were importantly increased in DOX group in accordance with previous studies findings when compared with control groups [8, 22].

The other effect of the DOX-induced oxidative stress occurs through free radicals via binding to lipids, proteins and nucleic acid-bases causing damage of cell viability, cell structure, cell membrane in this way [24]. At this point, level of the BUN and creatinine in serum is an important biochemical biomarker to evaluate the kidney function. In accordance with the previous studies, DOX strongly increased both the BUN and creatinine levels, indicating impaired glomerular filtration function [25, 26]. In the present study, we showed that DOX importantly increased creatinine and BUN levels in the rats. BUN and creatinine are one of the most commonly used laboratory tests to evaluate kidney damages, but rise above the normal threshold is not observed until more than 50% of renal function lost [27, 28]. Therefore, treatment with renoprotective agent is important before and after DOX administration.

In the present study, the 10 and 100 mg/kg quercetin treatment of before and after DOX injection effectively restored the level of all these parameters. In addition, the most effective reduction was seen in the high quercetin dose group. These results are in the line with the previous studies indicating the renoprotective effect of quercetin against cisplatin-induced renal toxicity [29-31], lead-induced nephrotoxicity in rat kidney [32], and nano zinc oxide-induced nephrotoxicity in rats [33].

[^{99m}Tc]Tc-DMSA renal cortical scintigraphy is a commonly used test for the detection of renal infection, subsequent cortical damage and for calculate relative renal function. It is a reliable test to show the effect of nephrotoxic agents on the kidney parenchyma [34, 35]. Studies have also displayed that [^{99m}Tc]Tc-DMSA renal cortical scintigraphy is a sensitive test that demonstrates the beneficial effect of renal protective agents on the nephrotoxicity [36,37]. In a study conducted by Hosseinimehr et al. [36], investigating the protective effect of thymol on the cisplatin-induced nephrotoxicity, reported that [^{99m}Tc]Tc-DMSA renal scintigraphy is a relevant technique for assessing nephrotoxicity and / or nephroprotective effect. In a similar study, Salihoğlu et al. [37] showed that the early renal damage was accurately displayed with [^{99m}Tc]Tc-DMSA renal scintigraphy. In another study, Aygun et al. [12] investigated the protective effect of melatonin and agomelatin on adriamycin-induced nephrotoxicity; found that [^{99m}Tc]Tc-DMSA plays an important role in the early detection of nephrotoxicity.

Previous studies showed that quercetin reduced doxorubicin-induced renal damage both histological and biochemical methods [38, 39].

It is important to investigate the methods that determine the early toxicity caused by the drugs used in chemotherapy. A pilot study demonstrated that ^{18}F-FDG and ^{67}Ga-citrate radiopharmaceuticals agent could identify early multi-organ toxicity induced by doxorubicin [40]. In this present study, we found that [^{99m}Tc]Tc-DMSA scintigraphy findings were compatible with biochemistry and tissue parameters in showing both nephrotoxicity and nephroprotective effects.

CONCLUSION

The results of the present study indicated that oxidative stress and inflammation are closely associated with DOX-induced nephrotoxicity. Intraperitoneally administered low and high dose of quercetin exhibits strongly renoprotective effect in DOX induced nephrotoxic rat model. In addition, [^{99m}Tc]Tc-DMSA scintigraphy results are consistent with biochemical results. [^{99m}Tc]Tc-DMSA scintigraphy management can be used in patients receiving DOX in the clinic and in experimental studies investigating nephrotoxicty.

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