



# The activity of *Terminalia chebula* Retz. extract on doxorubicin-induced renal damage in rats

[La actividad del extracto de *Terminalia chebula* Retz. sobre el daño renal inducido por doxorubicina en ratas]

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## Abstract

**Context:** Doxorubicin (DXR) is a common anticancer drug known to produce several complications. *Terminalia chebula* popularly known as 'King of medicine' is found to possess wound healing, anti-inflammatory and antioxidant properties.

**Aims:** To evaluate the effects of *Terminalia chebula* extract on doxorubicin-induced renal damages in rats.

**Methods:** Coadministration of *Terminalia chebula* extract (0.25, 0.5 and 1.0 g/kg) was tested against DXR (2.5 mg/kg) induced renal damages in rats. Additional two groups were evaluated by administering 0.5 g/kg of the extract to animals either before or after DXR treatment. Kidney function tests were performed by measuring the serum levels of urea, creatinine, uric acid, and total protein. The antioxidant activity of the extract was evaluated by *in vivo* and *in vitro* methods. Histopathology of kidney tissues was performed to assess the morphological changes. The significance of results obtained were statistically analyzed.

**Results:** The data obtained indicated that co-administration of the extract at higher doses (0.5 and 1.0 g/kg) significantly ( $p < 0.01$ ) reduces the serum levels of creatinine, urea, uric acid, and total proteins compared to DXR group. The extract also decreases the structural damages induced by DXR and exhibited antioxidant property. However, the pre- and post-treatments of *Terminalia* extract neither alter significantly the biomarker levels nor ameliorated the histopathological changes induced by DXR in rats.

**Conclusions:** The observations indicated that co-administration of *Terminalia chebula* decreased the renal damage induced by DXR in rats. The protective action of the extract may be related to its wound-healing and antioxidant properties, the latter of which diminished the free-radical damage induced by DXR.

**Keywords:** antioxidant; doxorubicin; renal damage; *Terminalia chebula*.

## Resumen

**Contexto:** La doxorubicina (DXR) es un medicamento común contra el cáncer que produce varias complicaciones. La *Terminalia chebula*, conocida popularmente como "Rey de la medicina", posee propiedades curativas, anti-inflamatorias y antioxidantes.

**Objetivos:** Evaluar los efectos del extracto de *Terminalia chebula* sobre daños renales inducidos por doxorubicina en ratas.

**Métodos:** La administración conjunta del extracto de *Terminalia chebula* (0,25; 0,5 y 1,0 g/kg) se probó contra daños renales inducidos por DXR (2,5 mg/kg) en ratas. Se evaluaron dos grupos adicionales administrando 0,5 g/kg del extracto a animales antes o después del tratamiento con DXR. Las pruebas de función renal se realizaron midiendo los niveles séricos de urea, creatinina, ácido úrico y proteína total. La actividad antioxidante del extracto se evaluó por métodos *in vivo* e *in vitro*. La histopatología de los tejidos renales se realizó para evaluar los cambios morfológicos. La importancia de los resultados obtenidos se analizó estadísticamente.

**Resultados:** La administración conjunta del extracto a dosis más altas (0,5 y 1,0 g/kg) significativamente ( $p < 0,01$ ) redujo los niveles séricos de creatinina, urea, ácido úrico y proteínas totales en comparación con el grupo DXR. El extracto también disminuyó los daños estructurales inducidos por DXR y exhibió propiedades antioxidantes. Sin embargo, los tratamientos previos y posteriores del extracto de *Terminalia* no alteraron significativamente los niveles de biomarcadores ni mejoraron los cambios histopatológicos inducidos por DXR en ratas.

**Conclusiones:** Las observaciones indicaron que la administración conjunta de *Terminalia chebula* disminuyó el daño renal inducido por DXR en ratas. La acción protectora del extracto puede estar relacionada con sus propiedades antioxidantes y de curación de heridas, la última de las cuales disminuyó el daño de los radicales libres inducido por DXR.

**Palabras Clave:** antioxidante; daño renal; doxorubicina; *Terminalia chebula*.

## ARTICLE INFO

Received: December 1, 2019.

Received in revised form: January 9, 2020.

Accepted: January 19, 2020.

Available Online: February 4, 2020.

Declaration of interests: The authors declare no conflict of interest.

Funding: This research was not funded and did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.



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## INTRODUCTION

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*Terminalia chebula* (Fam. *Combretaceae*) is an important plant in traditional systems of medicine. It is commonly known as black myrobalan in English and can be found in teak and mixed deciduous forests and the dry regions of the Asian subcontinent (Gupta, 2012).

The fruit of *Terminalia chebula* is held in high regard by folk medicinal practitioners (Fundter, 1992). Early studies indicated that *Terminalia chebula* has strong wound-healing, antimicrobial, and cardioprotective activities. Other therapeutic benefits related to the plants of *Terminalia chebula* include its antiaging, anticlastogenic, antitumor, antilithiatic, antihyperlipidemic, and radio protective activities (Rathinamoorthy and Thilagavathi, 2014).

The phytoconstituents of *Terminalia chebula* include hydrolysable tannins, which are considered to be responsible for its pharmacological activities, at contents that can vary from 20–50%. These tannins comprise phenolic carboxylic acids such as gallic acid, ellagic acid, and chebulic acid, as well as gallotannins such as 1,6-di-O-galloyl- $\beta$ -D-glucose, 3,4,6-tri-O-galloyl- $\beta$ -D-glucose, 2,3,4,6-tetra-O-galloyl- $\beta$ -D-glucose, and 1,2,3,4,6-penta-O-galloyl- $\beta$ -D-glucose. Ellagitannins such as punacalagin, casuarinin, corilagin, and terchebulin and other phenolic carboxylic acids such as chebulanin, neochebulinic acid, chebulagic acid and chebulinic acid have also been identified as hydrolysable tannins found in *Terminalia chebula* (Chattopadhyay and Bhattacharyya, 2007).

Doxorubicin (DXR) is an anthracycline anticancer drug that was first extracted from *Streptomyces peucetius var. caesioides* and is routinely used in the treatment of breast, lung, gastric, ovarian, and thyroid cancers, as well as non-Hodgkin's and Hodgkin's lymphoma and sarcomas. However, a major drawback of DXR is its cardiac, renal, pulmonary, testicular, and hematological toxicity (Carvalho et al., 2009).

There are two proposed mechanisms suggested for antineoplastic effect: firstly, by intercalation

into DNA and disruption of topoisomerase-II-mediated DNA repair; and secondly, by generation of free radicals and their resulting damage to cellular membranes, DNA, and proteins (Gewirtz, 1999).

Although the exact mechanism is unknown, it is believed that the nephrotoxicity of DXR may be mediated through free radical formation, iron-dependent oxidative damage of biological macromolecules, membrane lipid peroxidation, and protein oxidation. DXR-induced changes in the kidneys include increased glomerular capillary permeability and tubular atrophy (Wapstra et al., 1999).

This study was designed to evaluate the effect of *Terminalia chebula* extract on DXR-induced nephrotoxicity in rats. The effects were assessed under three different administration regimes, i.e., simultaneous co-administration, before treatment with DXR, and after treatment with DXR.

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## MATERIAL AND METHODS

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### Chemicals

A sample of the ethanolic extract of *Terminalia chebula* (TCE) was obtained from Sami Labs, Bangalore, India. The powder form of the extract was weighed, dissolved in distilled water, and administered orally according to the dose level and body weight of the animals.

### Animals

Eight-week-old healthy, laboratory bred, Wistar rats (male and female) weighing  $160 \pm 10$  g were maintained under standard laboratory conditions (12:12 h light/dark cycle) and provided with water and pellet food *ad libitum*. The experiments were conducted in an animal house approved by the Committee for the Purpose of Control and Supervision of Experiments on Animals (CPCSEA, Chennai, India) after obtaining prior approval from the Institutional Animal Ethics Committee (Approval # AACP/IAEC/P-45/2018). The animals were handled humanely, kept in plastic cages in a well ventilated and hygienic rat house under

suitable conditions of temperature ( $22 \pm 2^\circ\text{C}$ ) and humidity (50 - 60%). The animals were acclimatized in lab conditions for two weeks before starting the experiments. The unhealthy and pregnant animals were excluded from the study and returned to the central animal house for further care.

### Administration of doxorubicin

DXR was obtained as a research sample from GETWELL Pharmaceuticals, Gurgaon, India. A solution of DXR was prepared by dissolving the required amount in distilled water as per dosage. The freshly prepared DXR (2.5 mg/kg) was administered by the intra-peritoneal route. Each animal received a dose of DXR on alternate days for a period of 12 days (Vishwanatha et al., 2011).

### Dosage, treatment, and sampling

The experiment was performed on adult rats (6-8 animals). The animals were divided into normal control (saline solution at 5 mL/kg, 28 days), positive control (DXR, 12 days), negative control (TCE at 1 g/kg daily for 28 days), and treatment groups [DXR + TCE at 0.25, 0.5 or 1 g/kg (Sharma et al., 2011), daily for 28 days].

To investigate the effects of pre- and post-treatment with TCE, two additional groups were tested. In the pre-treatment group, TCE at 0.5 g/kg was administered daily for 16 days followed by 12 days of DXR (dosed on alternate days). In the post-treatment group, the schedule was reversed to 12 days of DXR (dosed on alternate days) followed by 16 days of TCE treatment (0.5 g/kg, daily).

### Kidney function tests

The kidney function tests were performed by measuring the creatinine, urea, uric acid, and total protein in the rat serum. Blood samples were collected from the retro-orbital plexus under mild ether anesthesia and the serum was separated.

### Urea

The principle of urea measurement involves the hydrolysis of urea in the presence of water and urease to produce ammonia and carbon dioxide.

Under alkaline conditions, the ammonia formed reacts with hypochlorite and phenolic chromogen to form colored indophenol, which absorbs light at 578 nm. Sodium nitroprusside acts as a catalyst. The protocol of the estimation includes addition of 10 g/L phenol, 0.05 g/L sodium nitroprusside, 5.0 g/L sodium hydroxide and 0.42 g/L sodium hypochlorite to 1 mL of the sample. The reaction mixture was allowed at room temperature for 30 minutes and the colored developed was measured spectroscopically. The intensity of the color is proportional to the concentration of urea in the sample (mg/dL) (Chaney and Marbach, 1962).

### Creatinine

Creatinine reacts with picric acid in an alkaline medium to form an orange colored complex. The rate of formation of this complex is measured by reading the change in absorbance at 505 nm, which is proportional to the concentration of creatinine. The method of estimation involved two reagents viz., reagent 1 and reagent 2. Reagent 1 contained 40 mM/L picric acid, 200 mM/L sodium hydroxide, surfactant and preservative in quantity sufficient (q.s) concentration. The reagent 2 (standard creatinine) contained 2 mg/dL creatinine and stabilizer, q.s. 1000  $\mu\text{L}$  of the reagent 1 solution was mixed with either 100  $\mu\text{L}$  of serum sample or 100  $\mu\text{L}$  of reagent 2 solution, the reaction mixture was incubated at  $37^\circ\text{C}$  for 5 minutes and the absorbance of the color developed was measured at 505 nm. The reaction time and the concentration of picric acid and sodium hydroxide have been optimized to avoid interference from ketoacids. Serum creatinine level is represented in mg/dL (Hawk et al., 1947).

### Uric acid

The basis of the estimation includes oxidation of uric acid to allantoin and hydrogen peroxide by the enzyme uricase. In presence of peroxidase, the hydrogen peroxide formed is coupled with an aniline derivative and 4-aminoantipyrene (4-AAP) to form a colored chromogen complex, the absorbance of which is measured at 550 nm and is proportional to the uric acid concentration in the sample (mg/dL). The protocol of the estimation

includes; reagent 1 (50 mmol/L tris buffer solution (pH 8.25), 120 U/L uricase, 0.2 mmol/L aniline derivative, 0.5 mmol/L 4-amino antipyrine and 500 U/L peroxidase) and reagent 2 [(standard uric acid) contained 6 mg/dL uric acid, stabilizer q.s and preservative q.s]. A volume of 1000  $\mu$ L of the reagent 1 was mixed with 20  $\mu$ L of sample/20  $\mu$ L of reagent 2, reaction was allowed for 5 minutes at 37°C and the absorbance was measured at 550 nm (Fossati et al., 1980).

### Total protein

According to the principle, peptide bonds of proteins react with cupric ions in alkaline solution to form a colored chelate, the absorbance of which is measured at 578 nm. The biuret reagent contains sodium potassium tartrate, which helps maintain the solubility of this complex under alkaline conditions. The absorbance of the complex is proportional to the concentration of total protein in the sample (g/dL). The procedure of the estimation was done as per the kit protocol. The reagent 1 contained 7 mM/L copper sulphate, 200 mM/L sodium hydroxide, 20 mM/L sodium-potassium tartrate and surfactant (q.s). The reagent 2 (standard protein) contained 6.5 g/dL bovine serum albumin and preservative (q.s). A volume of 1000  $\mu$ L of the reagent 1 was mixed with 10  $\mu$ L of serum sample or 10  $\mu$ L of standard protein solution (reagent 2). The reaction mixture was incubated at 37°C for 5 minutes and the absorbance was recorded (Kalpan and Lavemel, 1983).

### Kidney histopathology

The histopathological studies were performed by Deepak Diagnostics, Bangalore. Kidney samples were stained with periodic acid and Schiff's reagent after staining with hematoxylin and eosin. In brief the procedure includes dissection of kidney after sacrificing the animals under light ether anesthesia. The tissues were embedded in paraffin, standard section (6  $\mu$ m) were made and stained with hematoxylin and eosin G solution for 3 minutes. Before staining, the sections were deparaffinized in xylene and rehydrated with alcohol (70%). The stained slides were washed with distilled water and mounted with DPX mounting

media. The slides were observed microscopically (Nikon, Japan) for the histological characterization and photographed using Nikon DXM 1200 CC digital camera. The stained renal tissues were studied for glomerular congestion, glomerular atrophy, tubular atrophy, tubular dilatation, denudation and necrosis, cast formation, and interstitial inflammation (Fig. 1A-F) (Gamble, 1975).

### Serum reduced glutathione (GSH) measurement

GSH levels were measured according to the method of Ellman using 5,5'-dithio-bis-(2-nitrobenzoic acid) (DTNB, also known as Ellman's reagent). DTNB solution was added to the homogenate and the absorbance was measured at 412 nm. The procedure includes mixing 0.75 mL of sample with 0.75 mL of 4% sulfosalicylic acid and centrifugation at 1200  $\times$ g for 5 minutes (4°C). From this, 0.5 mL of supernatant was taken and added to 4.5 mL of 0.1 mM DTNB (5,5 dithiobis-2-nitro benzoic acid). The absorbance of the reaction mixture after 1 minute was measured and GSH level was expressed as  $\mu$ mol/g of wet tissue (Teitze, 1969).

### *In vitro* antioxidant activity

The *in vitro* antioxidant assay was done by the procedure of Ruch et al. (1989). In this method a 40 mM solution of the hydrogen peroxide was prepared in phosphate buffer (50 mM, pH 7.4). Different concentration of *T. chebula* and ascorbic acid (10 to 160  $\mu$ g/mL) were added to the hydrogen peroxide solution, the absorbance was recorded at 230 nm after allowing the mixture to stand for 15 minutes. The percentage scavenging activity was calculated from equation [1]. The IC<sub>50</sub> (50% inhibitory concentration) was calculated manually from the graph of concentration of test substance *versus* percentage inhibition.

$$\text{Percentage scavenging activity} = \frac{(\text{Abs of control} - \text{Abs of test})}{\text{Abs of control}} \times 100 \quad [1]$$

### Statistical analysis

Two-way ANOVA and Bonferroni comparison was performed for all groups. Two comparisons were made: normal control vs. DXR and DXR vs.

treatment groups. All values with a significance of  $p < 0.05$  were marked with an asterisk or superscript.

## RESULTS

### Effects of TCE on kidney function biomarkers in DXR-treated rats

The data indicated that administration of DXR (2.5 mg/kg) to the male rats increased the serum creatinine, urea, uric acid, and total protein levels significantly ( $p < 0.001$ ) compared to the control group. The concurrent administration of TCE in three doses resulted in a dose-dependent reduction in the levels of the renal function biomarkers. TCE at 0.5 g/kg produced a significant ( $p < 0.05$ ) reduction in the creatinine, uric acid, and total proteins levels compared to DXR group. Further, when the dose of TCE was increased (1 g/kg), more enhancement ( $p < 0.01$ ) in the inhibitory effect was observed. This dose of TCE also reduced ( $p < 0.05$ ) the serum urea levels when comparison was made with DXR data. The pre- and post-treatments with TCE (0.5 g/kg) did not cause sig-

nificant reduction on the levels of tested biomarkers. The administration of TCE to normal animals at 1 g/kg dose showed no-significant variation on the levels of the renal biomarkers compared to the control group (Table 1).

### Histopathological studies of kidney after the administration of TCE

The histopathological data indicated that administration of DXR (2.5 mg/kg) increased the glomerular congestion, glomerular atrophy, tubular atrophy, tubular dilatation, denudation, necrosis, cast formation in tubules, and interstitial inflammation in rats. A dose-dependent reduction in these parameters were observed when TCE was tested together with DXR. TCE at 0.5 and 1.0 g/kg was found to be highly effective in minimizing the damages induced by DXR. However, both pre- and post-treatments of TCE did not reduce the renal damages induced by DXR. Furthermore, the highest tested dose of TCE (1.0 g/kg) in normal animals did not produced any observable structural damage on the isolated renal tissues (Table 2 and Fig. 1A-F).

**Table 1.** Effects of ethanolic extract of *Terminalia chebula* (TCE) on kidney function biomarkers in DXR-treated rats.

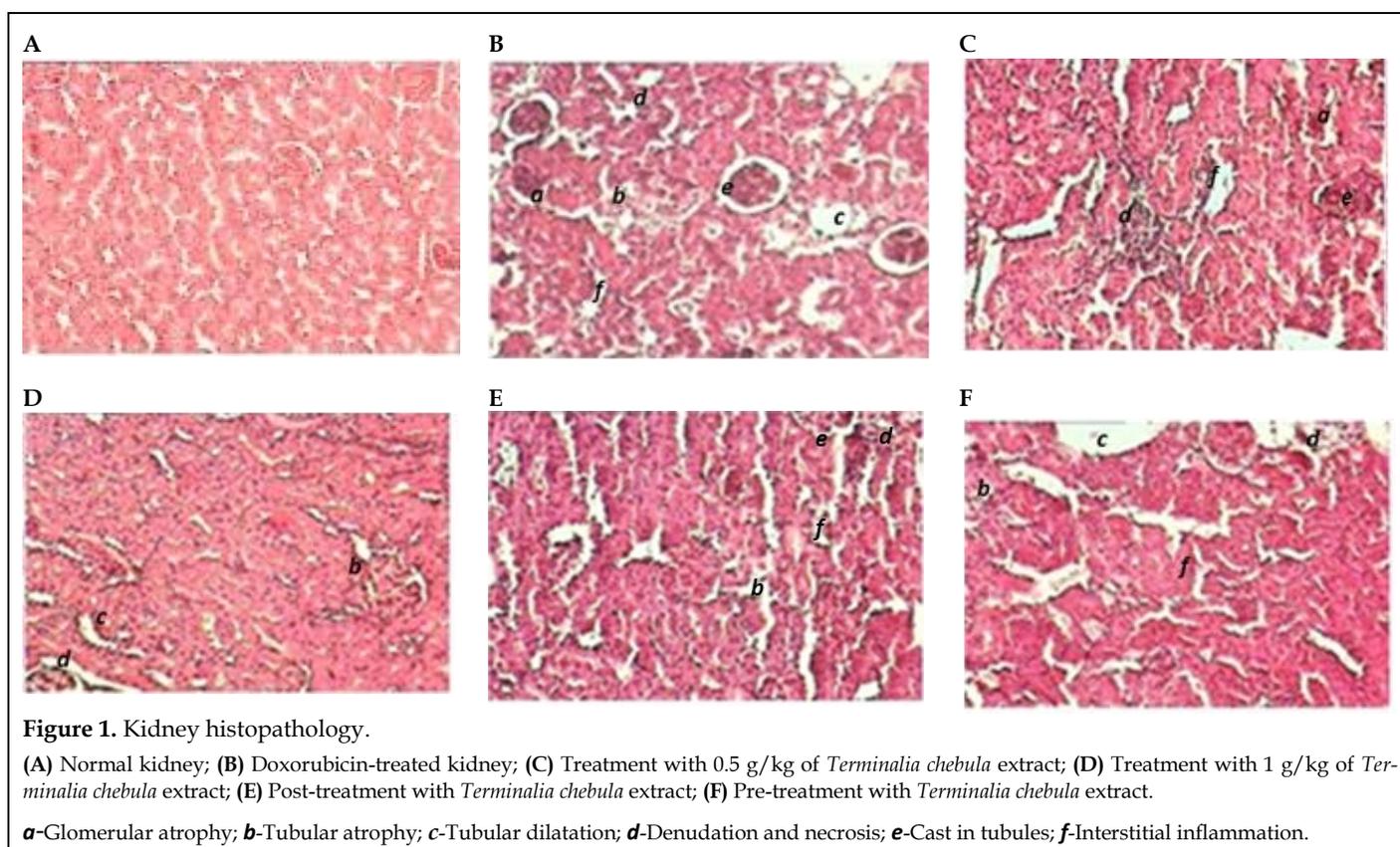
Treatment and dose	Dose	Creatinine (mg/dL)	Urea (mg/dL)	Uric acid (mg/dL)	Total protein (g/dL)
Control		0.36 ± 0.01	16.54 ± 4.05	1.97 ± 0.01	5.11 ± 0.02
<i>Terminalia chebula</i>	1 g/kg	0.26 ± 0.01	14.56 ± 3.94	2.58 ± 0.29	5.31 ± 0.09
Doxorubicin (DXR)	2.5 mg/kg	2.78 ± 0.02 <sup>a</sup>	52.62 ± 7.18 <sup>a</sup>	13.08 ± 0.02 <sup>a</sup>	6.93 ± 0.04 <sup>a</sup>
Group 1: Concurrent	DXR + TCE 0.25 g/kg	2.87 ± 0.01	51.13 ± 5.79	13.11 ± 0.04	6.59 ± 0.06*
Group 2: Concurrent	DXR + TCE 0.5 g/kg	2.32 ± 0.01*	47.11 ± 6.26	11.64 ± 0.04*	6.51 ± 0.07*
Group 3: Concurrent	DXR + TCE 1.0 g/kg	2.12 ± 0.04**	41.45 ± 5.49*	10.86 ± 0.08*	6.02 ± 0.14**
Group 4: Post-treatment	DXR + TCE 0.5 g/kg	2.75 ± 0.01	51.87 ± 5.73	12.54 ± 0.11	6.84 ± 0.09
Group 5: Pre-treatment	DXR + TCE 0.5 g/kg	2.65 ± 0.01	54.52 ± 6.94	13.22 ± 0.21	6.68 ± 0.06*

Values are represented as mean ± SEM; n= 6-8. Two-way ANOVA with Bonferroni comparison. <sup>a</sup> $p < 0.001$  compared to normal control, \* $p < 0.05$ , \*\* $p < 0.01$  compared to doxorubicin-treated animals.

**Table 2.** Histopathological observation of kidney tissue damage in both rats after *Terminalia chebula* (TCE) and/or doxorubicin (DXR) treatments.

Treatment and dose	Glomerular congestion	Glomerular atrophy	Tubular atrophy	Tubular dilatation	Denudation and necrosis	Cast in tubules	Interstitial inflammation
<b>Control</b>	-	-	-	-	-	-	-
<i>Terminalia chebula</i> (1 g/kg)	-	-	-	-	-	-	-
<b>Doxorubicin (DXR)</b> (2.5 mg/kg)	+++	+++	+++	+++	+++	+++	+++
<b>Group 1: Concurrent</b> (DXR + TCE 0.25 g/kg)	+++	+++	+++	+++	++	++	++
<b>Group 2: Concurrent</b> (DXR + TCE 0.50 g/kg)	++	++	++	++	+	+	+
<b>Group 3: Concurrent</b> (DXR + TCE 1.00 g/kg)	++	++	++	++	+	+	+
<b>Group 4: Post-treatment</b> (DXR + TCE 0.5 g/kg)	+++	++	+++	++	++	++	++
<b>Group 5: Pre-treatment</b> (DXR + TCE 0.5 g/kg)	+++	+++	+++	+++	++	++	++

(+++) Severe alteration, (++) Moderate alteration, (+) Mild alteration, (-) No alteration.

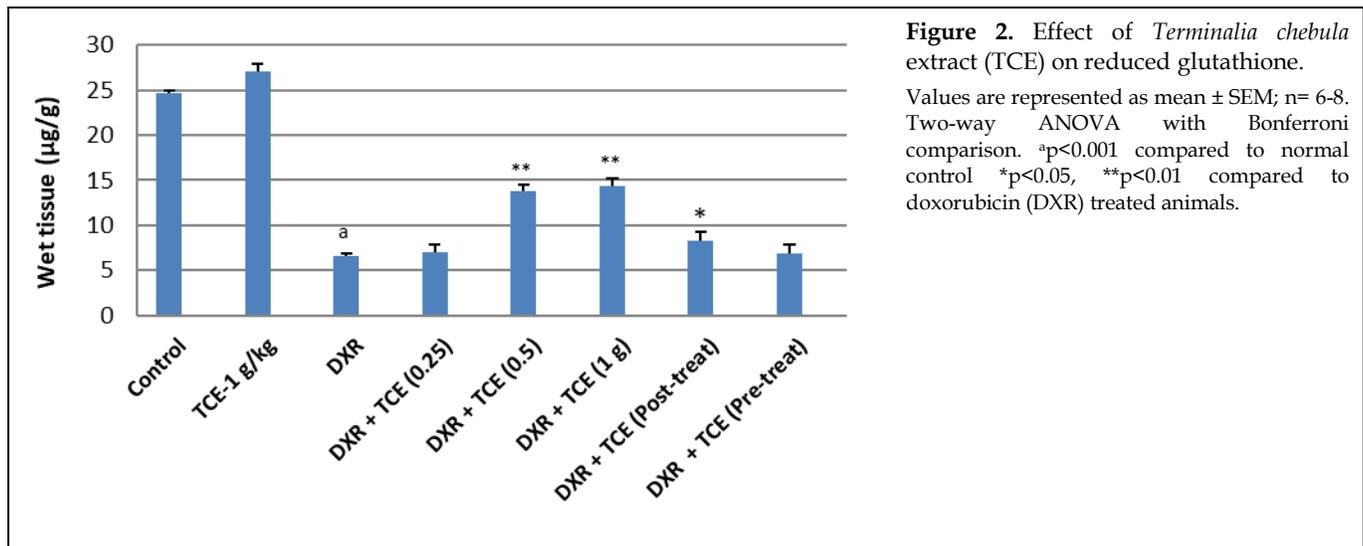


**Effects of TCE on serum GSH levels**

Administration of DXR resulted in significant ( $p < 0.001$ ) increase in the serum GSH levels compared to the control animals and TCE treatments was found to reduce these GSH level in a dose-dependent manner. TCE at 0.5 and 1 g/kg produced a significant ( $p < 0.01$ ) suppression of GSH level compared to the DXR group. In the pre and post treatment tests, only the pretreatment of TCE at 0.5 g/kg to the male rats was found to decrease ( $p < 0.05$ ) the GSH levels in the DXR animals. Administration of TCE (1 g/kg) to the normal animals did not showed any significant variation in the GSH levels when compared with control group (Fig. 2).

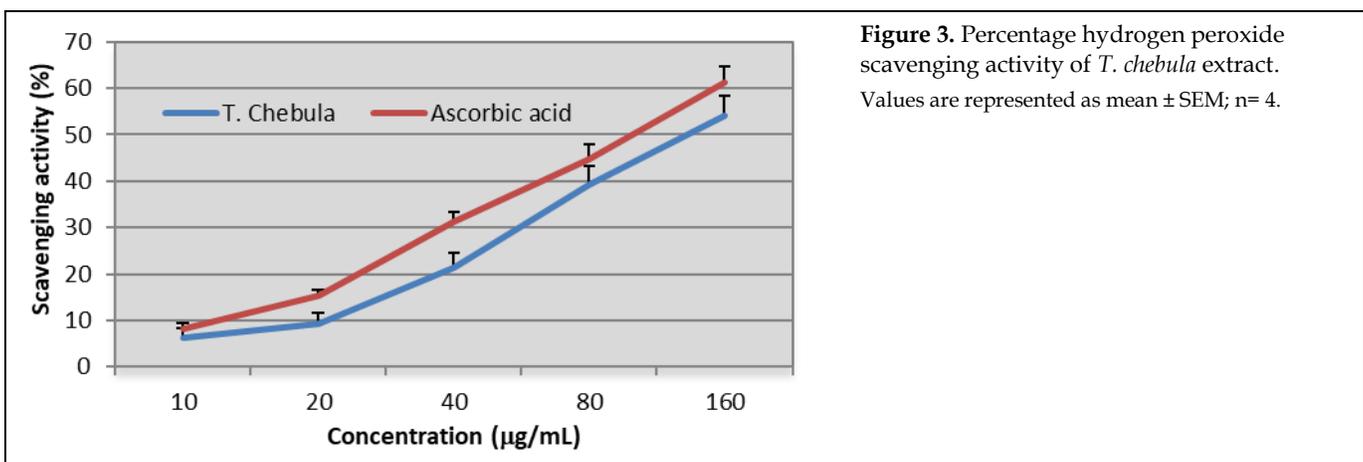
***In vitro* percentage hydrogen peroxide scavenging activity**

The percentage scavenging activity against the hydrogen peroxide free radicals was tested in five concentrations (10, 20, 40, 80 and 160  $\mu\text{g/mL}$ ). At the lowest tested dose (10  $\mu\text{g/mL}$ ) *T. chebula* produced 6.32 % scavenging activity and at highest dose (160  $\mu\text{g/mL}$ ) 54.23%. On the other hand, ascorbic acid at lowest tested dose showed 8.22% and at highest dose 61.28% scavenging activity. The  $\text{IC}_{50}$  values calculated from the graph indicated 125.4  $\mu\text{g/mL}$  and 112.6  $\mu\text{g/mL}$  for the *T. chebula* and ascorbic acid, respectively (Fig. 3).



**Figure 2.** Effect of *Terminalia chebula* extract (TCE) on reduced glutathione.

Values are represented as mean  $\pm$  SEM; n= 6-8. Two-way ANOVA with Bonferroni comparison. <sup>a</sup> $p < 0.001$  compared to normal control <sup>\*</sup> $p < 0.05$ , <sup>\*\*</sup> $p < 0.01$  compared to doxorubicin (DXR) treated animals.



**Figure 3.** Percentage hydrogen peroxide scavenging activity of *T. chebula* extract.

Values are represented as mean  $\pm$  SEM; n= 4.

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## DISCUSSION

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The present study demonstrated that administration of TCE significantly ( $p < 0.01$ ) decreased the elevated kidney function biomarker levels induced by DXR in rats (Table 1). Furthermore, a dose-dependent reduction in renal structure abnormalities was observed when TCE co-administered with DXR (Table 2). The TCE treatments were also found to improve the GSH levels in the DXR-treated animals and exhibited hydrogen peroxide scavenging activity (Figs. 2 and 3).

As discussed earlier, DXR is an anthracycline antibiotic that has been used for the treatment of cancer since 1969. The major disadvantage of this chemotherapeutic agent is that it causes various complications that affects cardiac, renal, pulmonary, and testicular tissues (Carvalho et al., 2009). In this study, it was observed that DXR administration increased the levels of creatinine, urea, uric acid, and total proteins in rats (Table 1). Previous research had revealed that administration of DXR causes renal damage and elevates the levels of markers concerned with the kidney function and the present study data is in agreement with these findings (Kamgang et al., 2012).

DXR is reported to cause cellular death through direct toxic effects to living cells and results in the release of a DXR-DNA complex into the intercellular space. This process prevents the release of cytokines and growth factors that otherwise participate in healing. Furthermore, DXR-induced increased oxidative stress is reported to damage macromolecules, membranes, and DNA, thereby contributing to cellular damage (Liu et al., 2007). Moreover, membrane lipid peroxidation, mitochondrial damage, iron-dependent oxidative damage to macromolecules, histamine release, and disruption of calcium homeostasis are also implicated in the mechanisms of drug related side effects (Wapstra et al., 1999). It is very likely that these mechanisms could have contributed in renal damages as well as the antioxidant defense depletion that was observed in the present research (Figs. 2 and 3).

Another observation of this study is that the co-administration of TCE with DXR produced a dose-dependent reduction in the levels of elevated renal biochemical markers in serum (Table 1). It was observed that TCE at both 0.5 and 1 g/kg reduced DXR-mediated renal damage (Table 2, Fig. 1C-D). To evaluate the effects of pre- and post-treatment of TCE on the DXR mediated renal damages, a single dose (0.5 g/kg) was tested in animals. The results from the study indicated that neither of these modes of TCE administration reduced significantly the renal complications induced by DXR (Tables 1, 2 and Fig. 1E-F).

*Terminalia chebula* is one of the most commonly used plants in traditional systems of medicine. Earlier studies revealed that administration of *Terminalia chebula* extract produced potent wound healing and antimicrobial effects (Suguna et al., 2002). Simultaneous administration of TCE in the present study appears to have had a similar effect in ameliorating the complications induced by DXR. In addition, it was suggested earlier that co-administration of an agent that possess antioxidant property may reduce the adverse effects of DXR, and this approach has been suggested to enhance patient compliance with the chemotherapeutic agent (Soliman et al., 2014). In this study, the data suggests that administration of TCE elevated the level of serum GSH as well scavenged the hydrogen peroxide molecules (Figs. 2 and 3), suggesting that TCE possess antioxidant potential. Similar observations have been reported previously where *T. chebula* was found to exhibit the antioxidant property by reducing the markers for oxidative stress such as serum levels of glutathione disulfide, lipid peroxidation and 2,2-diphenyl-1-picrylhydrazyl (DPPH) free radicals (Rathinamoorthy and Thilagavathi, 2014).

*Terminalia chebula* is known to contain several types of polyphenols. It has been reported that the antioxidant activity of a natural substance increases proportionally with the polyphenolic content, primarily because of their redox properties (Cheng, 2003). Polyphenols are reported to protect cellular constituents against destructive oxidative

damage, limiting the risks of degenerative diseases associated with oxidative stress by acting as potent free-radical scavengers. These studies suggest that antioxidant properties of polyphenols are related to their chemical structures and ability to donate/accept electrons, delocalizing unpaired electrons within their aromatic structures (Saha and Verma, 2016).

In summary, the observations from the present study indicates that *Terminalia chebula* decreased the renal complications associated with DXR administration and the possible mechanisms includes wound healing, antimicrobial and antioxidant properties.

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## CONCLUSIONS

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*Terminalia chebula* extract decreases the renal damage caused by DXR when it is administered simultaneously. Concurrent administration of the extract decreases DXR-mediated renal complications in rats. Further studies are required to evaluate the precise role of *Terminalia chebula* extract and to ensure DXR-chemotherapy-patient compliance.

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## CONFLICT OF INTEREST

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The authors declare no conflict of interest.

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## ACKNOWLEDGMENTS

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The authors declare his research was not funded and did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

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**AUTHOR CONTRIBUTION:**

Contribution	Muneer A	Alhowail A	Aldubayan M	Rabbani SI
Concepts or ideas				x
Design		x		
Definition of intellectual content			x	x
Literature search	x			
Experimental studies	x			
Data acquisition	x			
Data analysis		x		
Statistical analysis	x			x
Manuscript preparation		x	x	x
Manuscript editing		x	x	x
Manuscript review	x	x	x	x

**Citation Format:** Muneer A, Alhowail A, Aldubayan M, Rabbani SI (2020) The activity of *Terminalia chebula* Retz. extract on doxorubicin-induced renal damage in rats. *J Pharm Pharmacogn Res* 8(3): 237-246.