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ORIGINAL ARTICLE

Terminalia chebula Retz: A Prospective Agent in Reducing the Doxorubicin-Mediated Cardiotoxicity

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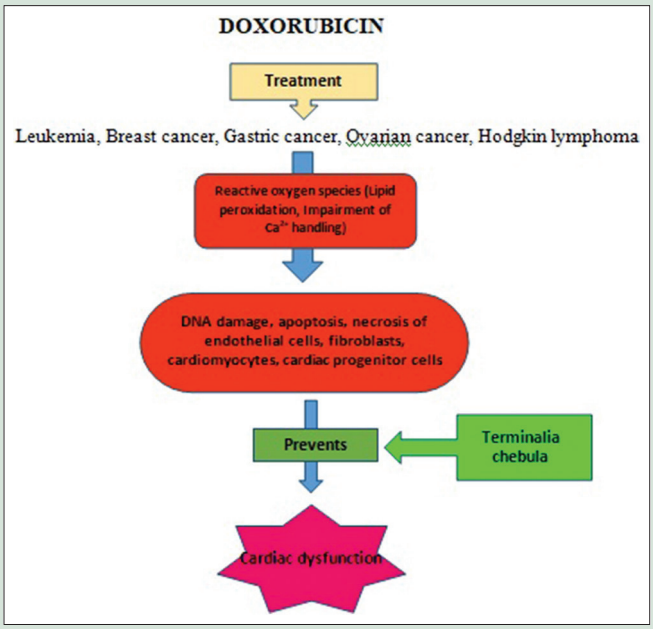
ABSTRACT

Objectives: The present study evaluated the role of *Terminalia chebula* Retz. extract against doxorubicin (DXR)-mediated cardiac damages in male and female rats. **Materials and Methods:** The ethanolic extract of *T. chebula* (0.25, 0.5, and 1 g/kg) was administered simultaneously with DXR (2.5 mg/kg, three-doses on alternate days by intraperitoneal route). Two additional groups were evaluated by administering 0.5 g/kg of the extract to animals before or after DXR treatment. The study was done separately in male and female adult Wistar rats of bodyweight 180–200 mg. The cardiac biomarker levels such as creatine kinase-monoenzyme B, lactate dehydrogenase, alanine aminotransferase, and aspartate aminotransferase were estimated after each treatment. Histopathology of cardiac tissue was studies analyzed, and the level of superoxide dismutase was determined in serum. The results were statistically analyzed using one-way ANOVA and Bonferroni tests and $P < 0.05$ was considered to indicate the statistical significance. **Results:** The observations indicated that DXR significantly ($P < 0.001$) elevated the biomarker levels of cardiac damage in both male and female rats, besides inducing the structural changes in the myocardium tissues and antioxidant status. The co-administration of higher doses of *T. chebula* extract (0.5 and 1 g/kg) with DXR significantly ($P < 0.01$) reduced the cardiac enzyme levels and histopathological changes and improve the antioxidant status compared to DXR group. Post-treatment with *T. chebula* (0.5 mg/kg) showed mild inhibitory action on the DXR-induced cardiac changes without significantly affecting the antioxidant level. **Conclusion:** The results suggest that co-administration of *T. chebula* reduced the DXR-mediated cardiac damages and the action could be related to the enhancement of the antioxidant property in rats.

Key words: Cardiac biomarkers, doxorubicin, oxidative stress, *Terminalia chebula*

SUMMARY

- Doxorubicin (DXR), a frequently used anticancer drug is known to produce myocardial complications in patients
- *Terminalia chebula* is conventionally used herbal medicine popular since ancient days
- In this study, *T. chebula* was tested at three doses such as 0.25, 0.5 and 1.0 mg/kg against the DXR (2.5 mg/kg)-induced cardiac damages in rats
- Histopathology of heart and serum antioxidant studies were done to evaluate the role of the treatments on the structure modification of myocardial cells and oxidant status, respectively
- A dose-dependent protective effect was observed on the level of cardiac damage markers when the data were compared between the DXR and *T. chebula* groups
- The effect was found to be marked at *T. chebula* – 1 mg/kg dose and the results were similar in both male and female rats
- A moderate level of protection was observed in the histological changes on myocardium and enhancement of serum superoxide dismutase level at 0.5 and 1 mg/kg dose of *T. chebula* in DXR animals
- The posttreated *T. chebula* showed mild inhibition on the cardiac biomarkers and histological changes induced by DXR with nonsignificant elevation in superoxide level. The study suggested that *T. chebula* protected the DXR-induced cardiac damages and the mechanism could be related to the wound-healing and antioxidant properties.



Abbreviations Used: *T. chebula*: *Terminalia chebula*, TCE: *Terminalia chebula* extract, DXR: Doxorubicin, CK-MB: Creatine kinase-MB, LDH: Lactate dehydrogenase, ALT: Alanine aminotransferase, AST: Aspartate aminotransferase, NAD: Nicotinamide adenine dinucleotide, MDH: Malate dehydrogenase, SOD: Superoxide dismutase, NBT: Nitro blue tetrazolium, EDTA: Ethylene diamine tetra acetic acid.

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INTRODUCTION

Through a variety of mechanisms, the heart is a target of injury for many drugs, both medically prescribed and otherwise. Drugs with potential cardiac toxicity are particularly prominent in cancer treatment and as

the survival of cancer patients continues to improve, drug toxicities feature more importantly in long-term patient outcomes.[1]

The anthracyclines like doxorubicin (DXR) are used to treat a wide range of hematologic and solid malignancies and are probably the most commonly recognized type of chemotherapy with known cardiac toxicity. Long-term cardiac toxicity manifests as ventricular dysfunction and clinical heart failure.[2]

The precise mechanism of cardiotoxicity of DXR is not clear. There are two main theories: iron-related free radicals and formation of doxorubicinol metabolite and mitochondrial disruption. One of the supporting evidence for the iron hypothesis is that the iron chelator, dexrazoxane is protective against DXR-induced toxicity *in vivo*. Risk of heart failure is directly related to cumulative dose and administration schedule. Finding a way to maintain the efficacy and reduce toxicity has been one of the major areas of focus of anthracycline research.[3]

A number of studies were conducted for antioxidants screening from natural medicine aiming to minimize oxidative injury by DXR. Several studies suggest that dietary supplementation with antioxidants can influence the response to chemotherapy as well as the development of adverse side effects resulting from antineoplastic treatment.[4]

Medicinal plants have been considered valuable and cheap source of unique phytoconstituents, which are used extensively in the development of drugs against various diseases. The World Health Organization reported that 80% of the world population relies chiefly on traditional medicines involving the use of plant extracts or their active constituents.[5]

Terminalia chebula Retz. is a flowering evergreen tree belonging to the family *Combretaceae*. It is well known as "haritaki" since it carries away all diseases or it is sacred to God Siva (Hara). The plant possesses enormous medicinal value and traditionally used for the treatment of various ailments for human beings.[6] The plant has been demonstrated to possess multiple pharmacological and medicinal activities, such as antioxidant, antimicrobial, antidiabetic, hepatoprotective, anti-inflammatory, antimutagenic, antiproliferative, radioprotective, cardioprotective, antiarthritic, anticaries, gastrointestinal motility, and wound-healing activity.[7] The extract was found to be used in the treatment of several psychological and psychiatric diseases in Iranian traditional medicine.[8] Terminalia extract was also reported to be effective in community-acquired infections.[9]

Although *T. chebula* is known to possess the antioxidant potential, its role in the prevention of DXR-mediated cardiac toxicity is not widely studied in the literature. Hence, the present research will evaluate the role of *T. chebula* extract on DXR-induced cardiac damage in Wistar rats. We tested three modes of the administration of extract, such as concurrent, pre- and posttreatment after DXR to assess the suitability in limiting the DXR-mediated complications.

MATERIALS AND METHODS

Chemicals

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

Animals

Eight week old healthy, laboratory bred, Wistar rats (male and female) weighing 160 ± 10 g were maintained under standard laboratory conditions (24°C ± 2°C, 12:12 h light/dark cycle) and provided water and pellet food *ad libitum*. The experiments were conducted in (Committee for the purpose of control and supervision of experiments on animals, Chennai, India) approved animal house after obtaining the prior approval from the Institutional Animal Ethics Committee.

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 of DXR in distilled water as per dosage. A freshly prepared DXR (2.5 mg/kg) was administered by the intraperitoneal route. On alternate days, each animal received a dose of DXR for a period of 12 days.[10]

Dosage, treatment, and sampling

The experiment was done separately on male and female rats, comprising 6–8 animals. The animals were grouped as normal control (saline – 5 mL/kg, 28 days), positive control (DXR, 12 days), negative control (TCE – 1 g/kg, daily for 28 days), and treatment group (DXR + TCE – 0.25, 0.5, and 1 g/kg,[11] daily for 28 days).

To find the effect of pre- and post-treatment of TCE, two additional groups were tested. In the pretreatment, TCE – 0.5 mg/kg was administered daily for 16-day followed by 12-day of DXR (6-doses on alternate days). In the posttreatment group, the schedule was reversed such as 12-day of DXR followed by 16-day of TCE (0.5 mg/kg, daily).

Markers for heart damage

Creatine kinase monoenzyme B (CK-MB), lactate dehydrogenase (LDH), alanine aminotransferase (ALT), and aspartate aminotransferase (AST) were used as biochemical markers for assessing the cardiac damage. The estimation of these biomarkers was done in serum separated from blood withdrawn under light ether anesthesia from retro-orbital plexus of rats.

Creatine kinase-monoenzyme B activity

The principle depends on incorporation of an antibody into the CK reagent. This antibody will bind to and inhibit the activity of the M sub-units of CK-MB. This means that only the activity of the B subunits of the serum is measured. If the activity is multiplied by a factor of 2, it gives the activity of CK-MB in serum (units/L).[12]

Lactate dehydrogenase estimation

LDH catalyzes the conversion of pyruvate to lactate with simultaneous oxidation of reduced nicotinamide adenine dinucleotide [reduced] (NADH) to nicotinamide adenine dinucleotide (NAD). The rate of decrease in absorbance due to the formation of NAD is measures at 340 nm and is proportional to the LDH activity in the sample (units/L).[13]

Alanine aminotransferase estimation

ALT catalyzes the transamination of L-alanine and α-ketoglutarate to form pyruvate and L-glutamate. In subsequent reaction, LDH reduces pyruvate to lactate with simultaneous oxidation of NADH to NAD. The rate of oxidation of NADH is measured kinetically by monitoring the decrease in absorbance at 340 nm. LD rapidly and completely reduces endogenous sample pyruvate during the initial incubation period, and hence that it does not interfere with the assay. Serum ALT values are represented as units/L.[14]

Aspartate aminotransferase estimation

AST catalyzes the transamination of L-aspartate and α-ketoglutarate to form L-glutamate and oxaloacetate. In subsequent reaction, malate dehydrognase

reduces oxaloacetate to malate with simultaneous oxidation of NAD. The rate of oxidation of NADH is measured kinetically by monitoring the decrease in absorbance at 340nm and is directly proportional to AST activity in the sample. LDH is added to enzyme system to prevent endogenous pyruvate interference, which is normally present in the serum (units/L).[15]

Histopathology

The histopathological studies were done in Deepak Diagnostics, Bangalore. Heart samples were stained with hematoxylin and eosin.[16] The cardiac tissue was studied for myocardial edema, myocardial inflammation, separation of fibers, and loss of striations [Figures 1-6].

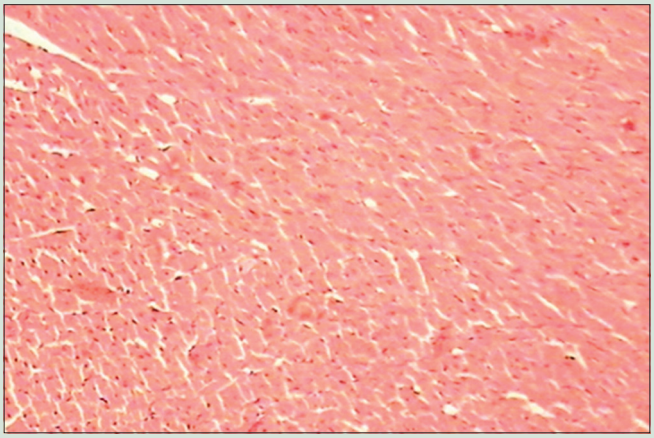


Figure 1: Histopathology of cardiac cells: Normal heart

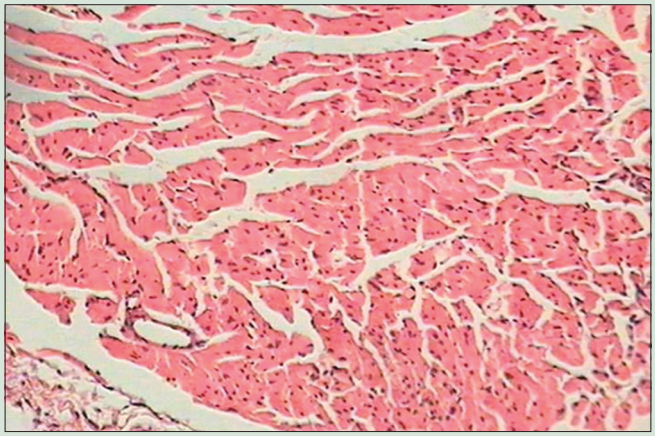


Figure 2: Histopathology of cardiac cells: Doxorubicin treated heart

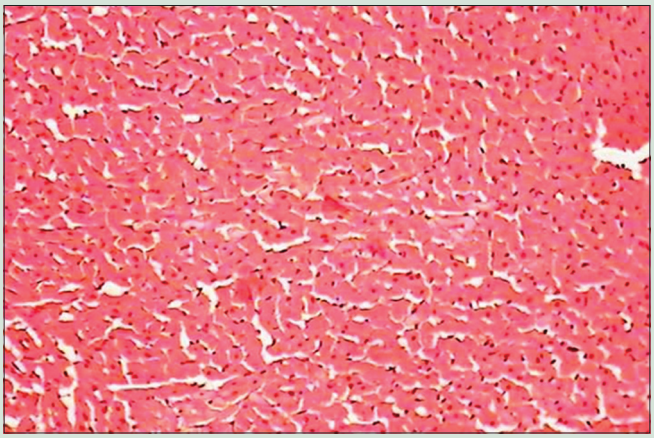


Figure 3: Histopathology of cardiac cells: Treatment with 0.5 g/kg of *Terminalia chebula* extract

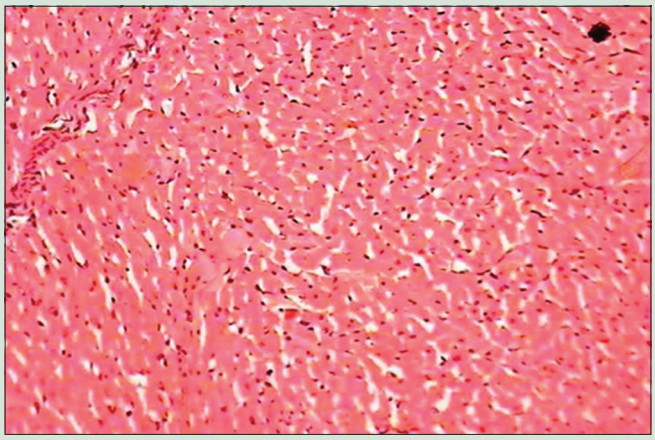


Figure 4: Histopathology of cardiac cells: Treatment with 1 g/kg of *Terminalia chebula* extract

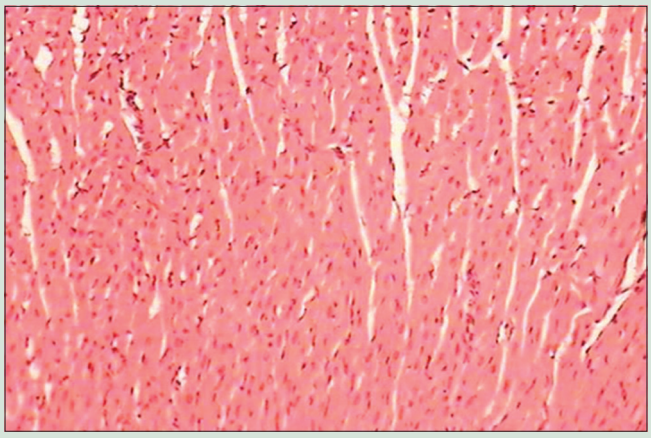


Figure 5: Histopathology of cardiac cells: Posttreatment with *Terminalia chebula* extract

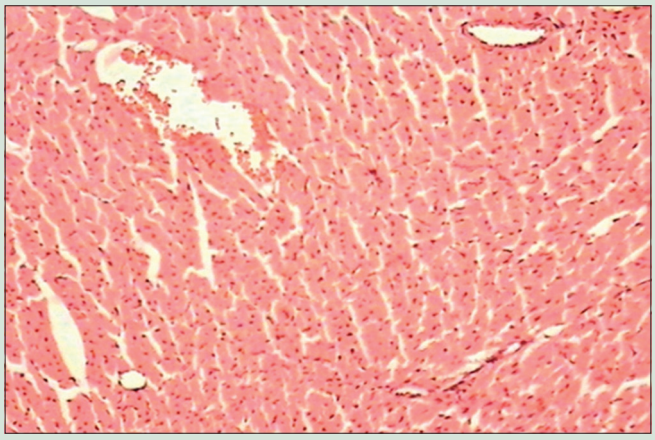


Figure 6: Histopathology of cardiac cells: Pretreatment with *Terminalia chebula* extract

Serum superoxide dismutase

The superoxide dismutase (SOD) activity is determined by the ability of the enzyme to inhibit auto oxidation of hydroxylamine at pH 10.2, which was accompanied by reduction of nitro blue tetrazolium and the nitrite produced in the presence of ethylene diamine tetra acetic acid was detected colorimetrically. The values were calculated as units/mg of protein.[17]

Statistical analysis

Two-way ANOVA and Bonferroni comparison was made for all groups. Two comparisons were made- normal control v/s DXR and DXR v/s treatment groups. All values with significance $P < 0.05$ are shown with an asterisk or superscript.

RESULTS

Effect of *Terminalia chebula* on cardiac biomarker levels in doxorubicin-treated male rats

Our study on serum cardiac biomarker estimation indicated that DXR at 2.5 mg/kg significantly ($P < 0.001$) elevated CK-MB, LDH, ALT and AST levels compared to the control animals. A dose-dependent suppression in the level of these enzymes was observed when TCE was tested at 0.25, 0.5, and 1.0 g/kg. Concurrent administration of TCE at 0.25 mg reduced significantly ($P < 0.05$) the ALT levels, while TCE at 0.5 reduced LDH and AST levels in addition to ALT ($P < 0.01$) compared to DXR treatment. The higher dose of TCE (1 g/kg) showed further decrease ($P < 0.01$) in the level of LDH, ALT, AST, and also suppressed CK-MB ($P < 0.05$) in comparison with DXR. The pre- and post-treatment data indicated that only the post-administration of TCE reduced the level of LDH and AST ($P < 0.05$) compared to challenge group and the rest of the values were insignificantly varied compared to DXR-treated group. Administration of highest tested dose of TCE (1 mg) to control animals however did not alter significantly the level of biomarker enzymes [Table 1].

Effect of *Terminalia chebula* on cardiac biomarker levels in doxorubicin-treated female rats

The observation from the female rats is in confirmation with the data from male rats that DXR elevated the level of cardiac biomarkers significantly ($P < 0.001$) compared to the control animals. The values for the administration of TCE suggested a dose-dependent decrease in the level of marker enzymes. TCE at 0.5 mg significantly ($P < 0.05$) reduced the level of LDH, ALT, and AST, whereas TCE at 1.0 g further reduced ($P < 0.01$) these enzyme levels and also exhibited a reduction in the level of CK-MG ($P < 0.05$) compared to the DXR group. The posttreatment data suggest that the administration of TCE reduced significantly ($P < 0.05$) the level of LDH, ALT, and AST compared to the challenge group. However, pre-treatment of TCE, as well as TCE in control animals, did not produce significant variation in the level of marker enzymes [Table 2].

Histopathology of cardiac tissue in both male and female rats

Four types of structural changes such as myocardial edema, myocardial inflammation, separation of fibers, and loss of striations were evaluated to study the histopathological changes in the heart. Our observation indicated that the administration of DXR produced a severe alteration in all the four types of parameters tested for structural changes. Administration of TCE at 0.5 and 1 g was found to reduce the changes to moderate level when compared to DXR group. The posttreatment of TCE showed a reduction in the myocardial inflammation and loss of striation to moderate levels, whereas other parameters as well as pretreatment of TCE did not change the structural deformities from severe levels. However, TCE in the control group did not alter the myocardial structural arrangement at the tested dose of 1 g/kg [Table 3].

Table 1: Effect of *Terminalia chebula* on cardiac biomarker levels in doxorubicin treated male rats

Treatment and dose	CK-MB (Units/L)	LDH (Units/L)	ALT (Units/L)	AST (Units/L)
Control	714.4±16.94	813.4±27.56	0.84±0.01	109.9±1.51
Terminalia chebula (1 g/kg)	732.1±15.46	706.9±11.19	0.79±0.03	104.2±1.65
DXR (2.5 mg/kg)	3759±133.83[a]	2870±51.62[a]	1.23±0.02[a]	390.6±3.2[a]
Group-1: Concurrent (DXR + TCE 0.25 g/kg)	3506±56.89	2913±46.69	1.14±0.01*	372.5±0.48
Group-2: Concurrent (DXR + TCE 0.5 g/kg)	3481±85.10	2340±37.81*	1.06±0.01**	310.7±0.29*
Group-3: Concurrent (DXR + TCE 1.0 g/kg)	2823±57.60*	2050±53.01**	1.05±0.01**	295±1.45**
Group-4: Post-DXR (DXR + TCE 0.5 g/kg)	3783±40.23	2452±46.42*	1.08±0.02**	307.5±4.57*
Group-5: Pre-DXR (DXR + TCE 0.5 g/kg)	3644±84.38	2701±56.22	1.20±0.02	301.6±6.25

Values are represented as Mean±SEM; n=6. Statistics: Two-way ANOVA with Bonferroni comparison. [a]P<0.001 compared to normal control, *P<0.05, **P<0.01 compared to Doxorubicin treated animals. DXR: Doxorubicin; TCE: *Terminalia chebula* extract; SEM: Standard error of mean; CK: Creatine kinase-MB; LDH: Lactate dehydrogenase; ALT: Alanine aminotransferase; AST: Aspartate aminotransferase

Table 2: Effect of *Terminalia chebula* on cardiac biomarker levels in doxorubicin treated female rats

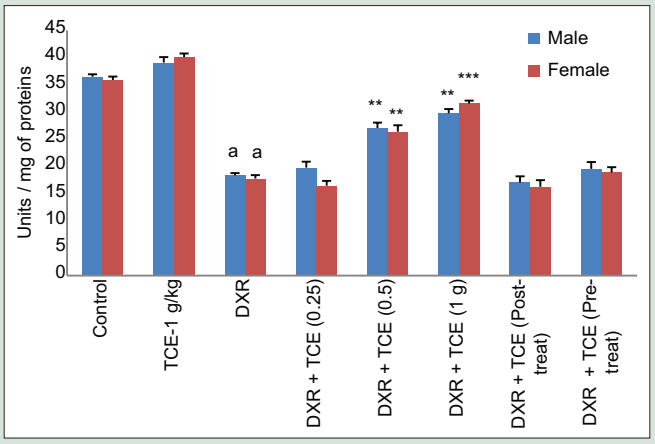
Treatment and dose	CK-MB (Units/L)	LDH (Units/L)	ALT (Units/L)	AST (Units/L)
Control	573.2±86.47	776.9±16.03	0.81±0.01	101.2±1.43
Terminalia chebula (1 g/kg)	751.6±16.52	676.5±2.75	0.79±0.02	101.3±2.21
DXR (2.5 mg/kg)	3671±58.89[a]	2622±54.56[a]	1.16±0.01[a]	370.8±0.88[a]
Group-1: Concurrent (DXR + TCE 0.25 g/kg)	3521±42.49	2527±50.96	1.13±0.01	374.7±1.50
Group-2: Concurrent (DXR + TCE 0.5 g/kg)	3488±53.38	2263±35.37*	1.05±0.01*	293.2±0.48*
Group-3: Concurrent (DXR + TCE 1.0 g/kg)	3195±37.52*	1955±49.72**	0.91±0.01**	274.9±1.81**
Group-4: Post-DXR (DXR + TCE 0.5 g/kg)	3644±26.54	2317±33.75*	1.00±0.03*	291.5±11.72*
Group-5: Pre-DXR (DXR + TCE 0.5 g/kg)	3599±57.48	2569±53.52	1.12±0.04	368.6±4.27

Values are represented as Mean±SEM; n=6. Statistics: Two-way ANOVA with Bonferroni comparison. [a]P<0.001 compared to normal control, *P<0.05, **P<0.01 compared to Doxorubicin treated animals. DXR: Doxorubicin; TCE: *Terminalia chebula* extract; SEM: Standard error of mean; CK: Creatine kinase-MB; LDH: Lactate dehydrogenase; ALT: Alanine aminotransferase; AST: Aspartate aminotransferase

Table 3: Histopathology of cardiac tissue in both male and female rats

Treatment and dose	Myocardial edema	Myocardial inflammation	Separation of fibers	Loss of striation
Control	-	-	-	-
Terminalia chebula (1 g/kg)	-	-	-	-
DXR (2.5 mg/kg)	+++	+++	+++	+++
Group-1: Concurrent (DXR + TCE 0.25 g/kg)	+++	+++	+++	+++
Group-2: Concurrent (DXR + TCE 0.5 g/kg)	++	++	++	++
Group-3: Concurrent (DXR + TCE 1.0 g/kg)	++	++	++	++
Group-4: Post-DXR (DXR + TCE 0.5 g/kg)	+++	++	+++	++
Group-5: Pre-DXR (DXR + TCE 0.5 g/kg)	+++	+++	+++	+++

+++: Severe alteration; ++: Moderate alteration; +: Mild alteration; -: No alteration; DXR: Doxorubicin; TCE: *Terminalia chebula* extract



Graph 1: Effect of *Terminalia chebula* extract on serum superoxide dismutase levels. Values are represented as mean ± standard error of mean; $n = 6$. Statistics: Two-way ANOVA with Bonferroni comparison. $^{a}P < 0.001$ compared to normal control. $^{**}P < 0.01$, $^{***}P < 0.001$ compared to DXR treated animals

Effect of *Terminalia chebula* extract on serum superoxide dismutase levels

The antioxidant activity of the extract is summarized in Graph 1. The data indicated that DXR in both male and female rats showed statistically significant ($P < 0.001$) reduction in the level of serum SOD compared to the control group. Administration of TCE at both 0.5 and 1 g/kg exhibited a significant ($P < 0.01$) in the level of serum SOD compared to the DXR group. The pre- and post-treatment as well as TCE at 0.25 (concurrent group) did not vary significantly the serum SOD levels in comparison with DXR animals. The highest tested dose of TCE showed insignificant elevation in the level of SOD at 1 g/kg in both male and female rats.

DISCUSSION

The present study indicated that co-administration of *T. chebula* extract (TCE) with DXR reduced dose-dependently the elevated cardiac biomarker levels, the highest tested doses (0.5 and 1 g/kg) was found to be effective in both male and female rats. The pre- and posttreatment group data suggest that TCE showed insignificant reduction in the cardiac enzyme levels [Tables 1 and 2]. Similar observations were found when the histopathology of the cardiac tissue was examined, where only the co-administration of TCE was found to be effective in reducing the structural changes induced by DXR but not the pre- and posttreatments of TCE [Table 3 and Figures 1-6]. The antioxidant analysis revealed that TCE's simultaneous administration enhanced the suppressed serum SOD level in DXR-treated rats [Graph 1].

The anthracycline antibiotic DXR is an important antineoplastic agent because of its high antitumor efficacy in hematological as well as in solid malignancies. However, its use is limited by the frequent induction of dose-dependent chronic cardiomyopathy.[3] The mechanisms of DXR cardiotoxicity include: (a) the formation of free reactive oxygen radicals, (b) direct DNA damage and/or interference with DNA repair, and (c) induction of immune reactions involving antigen-presenting cells in the heart.[18] Considering these complications, it has been suggested that the estimation of cardiac biomarkers levels should be done regularly if the patients are treated with DXR.[2] The data from the present study indicated that DXR-treated both male and female rats showed increased levels of cardiac enzymes, structural changes [Tables 1-3 and Figures 3 and 4] confirming with the earlier findings[3] and also suggesting that DXR have similar cardiac damaging potential in both male and female rats.

Among the various mechanisms discussed earlier for DXR, elevation in the oxidative stress is reported to be one of the important pathological conditions that contribute to the cardiac toxicity. The DXR-mediated oxidative stress has the potency to damage macromolecules, membranes and DNA, thereby contributing to cellular damage, energetic deficit, and acceleration of cell death through apoptosis and necrosis.[4] Further, membrane lipid per oxidation, mitochondrial damage, iron-dependent oxidative damage to macromolecules, histamine release, and disruption of calcium homeostasis are also implicated in the mechanism of drug-related side effects.[19] Our observation is in accordance with these findings that DXR elevated oxidative stress [Graph 1], and the cardiac damages could involve the mechanisms as discussed.

T. chebula known from the ancient times as a "king of medicine" and is an important component in several Ayurvedic preparations. *T. chebula* contains several medicinally important chemical constituents like tannins, polyphenols, carbohydrates, flavonols, glycosides, and triterpenoids. Some of the important components isolated aregallic acid, ellagic acid, chebulic acid and gallotannins, punacalagin, casurarinin, corilagin and terchebulin and others such as chebulanin, neochebulinic acid, chebulagic acid, and chebulinic acid.[20] These constituents are reported to possess anticancer, cardiotonic, anticlastogenic, and antioxidant properties. Tannins and glycosides were found to possess cardiotonic potential, flavonoids exhibit anticancer and antimutagenic activities, polyphenols can produce antioxidant effect.[7] Possibly due to the presence of these vital chemical constituents, co-administration of TCE with DXR in our study reduced the biochemical markers of the heart [Tables 1 and 2] and elevated the antioxidant status [Graph 1] along with minimizing the structural changes in the myocardium [Table 3].

The latest trend in DXR research is to minimize complications and improve the patient compliance. One of the areas where the research is now focused is to administer a known antioxidant with DXR so that the complications can be reduced to manageable levels.[21] Already there are reports that suggest administration of tocopherol, palmitic acid, and linoleic acid have shown promising results in reducing the cardiac complications of anthracycline antibiotics.[22] Since *T. chebula* being

an antioxidant also reported to possess anticancer, antimutagenic and cardiotonic activities, co-administration of TCE with DXR could show remarkable prognosis with DXR chemotherapy.

CONCLUSION

The present study indicated that co-administration of ethanolic TCE reduced the serum biomarker levels indicative of cardiac damage and structural changes induced by DXR. The preventing effect could be related to the antioxidant potential of *T. chebula*. Further research is suggested to find the suitability of using the *T. chebula* for improving the compliance in patients treated with DXR.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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