



## **Protective Effect of *Terminalia chebula* Extract in Doxorubicin Induced Hyperlipidemic Rats**

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### **Authors' contributions**

*This work was carried out in collaboration between both authors. Author AM performed the experiment and statistical analysis and author SIR designed the study, wrote the protocol and wrote the first draft of the manuscript. Both authors read and approved the final manuscript.*

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### **ABSTRACT**

**Aim:** To study the anti-hyperlipidemic activity of *Terminalia chebula* in rats.  
**Study Design:** Hyperlipidemia was induced by administering doxorubicin and the effect of *Terminalia chebula* was studied in male and female rats.  
**Methodology:** Three doses of hydroalcoholic extract of *Terminalia chebula* (0.25, 0.5 and 1.0 gm/kg, body weight, per orally for 28 days) was tested against the doxorubicin (0.25 mg/kg, intraperitoneal, 6 doses for 12 days) in male and female rats. Serum levels of total cholesterol, triglycerides, low-density lipoprotein (LDL-cholesterol) and high-density lipoprotein (HDL-cholesterol) were estimated. The antioxidant effect was determined by estimating the serum peroxidation levels. The result of the data was analyzed statistically by One-way Anova followed by Bonferroni comparison test.  $p < 0.05$  was considered to indicate the significance of the results.  
**Results and Discussion:** The data indicated that a dose-dependent significant ( $p < 0.05$ ) reversal was observed in the doxorubicin-induced elevated total cholesterol, triglycerides, LDL-cholesterol and diminished HDL-cholesterol upon treatment with *Terminalia chebula* in male rats. In the female

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rats, only the highest tested dose of *Terminalia chebula* (1 gm/kg) produced the inhibitory effect in the elevated lipid levels without affecting significantly the HDL-cholesterol activity. Further, when *Terminalia chebula* was tested separately at 0.5 g before and after the administration of doxorubicin, a significant inhibition was observed in the post treatment in both sexes. Serum lipid peroxidation was found to be significantly ( $p<0.05$ ) reduced by the extract compared to the doxorubicin group.

**Conclusion:** The results suggest that *Terminalia chebula* extract might have the potential to reduce doxorubicin-induced hyperlipidemic complications if administered together or after the doxorubicin therapy.

**Keywords:** Doxorubicin; *Terminalia chebula*; hyperlipidemia; lipid peroxidation.

## 1. INTRODUCTION

From ancient era medicinal plants are considered as the part and parcel of human society. Many species of plants are used medicinally mainly as herbal preparations in the indigenous medicine in the treatment of several diseases. *Terminalia chebula* is a flowering tree belonging to the family *Combretaceae* [1].

*Terminalia chebula* (*T. chebula*) is a branched deciduous tree. The fruits of the plant are reported to be used as an astringent, laxative, stomachic, tonic, anthelmintic and to cure gum bleeds [2]. The active constituents of the fruits are chebulinic acid, chebulagic acid, terchebulin and ellagic acid. The fruit extract was found to suppress oxidative stress and known to possess cardiotoxic, hepatoprotective and nephroprotective activities [3].

Doxorubicin (DOXO) is an anthracycline antibiotic obtained by hydroxylation of Daunorubicin. Doxorubicin is a common chemotherapeutic agent in the treatment of cancer. It causes breaks in DNA strands by activating Topoisomerase II and generating several type free radicals [4].

DOXO is reported to produce cardiotoxicity and nephrotoxicity as a unique adverse effect. Congestive heart failure due to cardiomyopathy occurs which might cause fatalities. Marrow depression, alopecia, stomatitis, vomiting and local tissue damage are other common adverse effects. DOXO toxicity is related to its ability to generate free radicals [5]. This toxicity is dissociable from its anticancer activity, making the drug usage limited and can also increase the adverse effects in cancer patients. In addition, DOXO can modify the lipid profile of the patient contributing to several cardiovascular related complications [6].

Earlier studies had reported that extract of *T. chebula* has hypolipidemic activity in experimentally induced atherosclerosis [7], however, its role in minimizing the adverse effects of DOXO such as hyperlipidemia was poorly studied in the literature. Hence, this study was designed to evaluate the effect of aqueous extract of *Terminalia chebula* on DOXO-induced hyperlipidemia in experimental animals by testing in three patterns such as simultaneous administration of extract with doxorubicin, prior to DOXO administration and after DOXO treatment.

## 2. MATERIALS AND METHODS

### 2.1 Chemicals

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 depending on the dose and body weight of the animals.

### 2.2 Animals

Eight week old healthy, laboratory bred, Wistar rats (male and female) weighing  $160\pm 10$  g were maintained under standard laboratory conditions ( $24\pm 2^\circ\text{C}$ , 12:12 h light / dark cycle) and provided water and pellet food *ad libitum*.

### 2.3 Administration of Doxorubicin

Doxorubicin (DOXO) was obtained as a research sample from GETWELL Pharmaceuticals, Gurgaon, India. A solution of DOXO was prepared by dissolving the required amount of DOXO in distilled water as per dosage. A freshly prepared DOXO (2.5 mg/kg) was administered by the intra- peritoneal route. On alternate days, each animal received a dose of DOXO for a period of 12 days [8].

## 2.4 Dosage, Treatment and Sampling

The experiment was done separately on male and female rats, comprising of 6-8 animals. The animals were grouped as normal control (saline – 5 ml/kg, 28 days), positive control (DOXO, 12 days), negative control (TCE – 1 g/kg, daily for 28 days) and treatment group (DOXO + TCE – 0.25, 0.5 and 1 g/kg [9], daily for 28 days).

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

## 2.5 Lipid Profile Estimation

Blood was drawn from retro-orbital plexus under light ether anesthesia. Lipid profile includes the estimation of total cholesterol, triglycerides, HDL-cholesterol and LDL-cholesterol. The estimations were done by using commercially available diagnostic kit (Span Diagnostic Ltd, Surat, India). In brief, the principle and procedure include;

### A. Triglycerides (TGs)

The principle behind estimation of triglycerides is the hydrolysis TGs by lipoprotein lipase (LPL) to produce glycerol and free fatty acid (FFA). In presence of glycerol kinase (GK), adenosine triphosphate (ATP) phosphorylates glycerol to produce glycerol 3-phosphate and adenosine diphosphate (ADP). Glycerol 3-phosphate is further oxidized by glycerol 3-phosphate oxidase (GPO) to produce dihydroxyacetone phosphate (DAP) and H<sub>2</sub>O<sub>2</sub>. In presence of peroxidase (POD), hydrogen peroxide couples with 4-aminoantipyrine (4-AAP) and 4-chlorophenol to produce red quinoneimine dye. Absorbance of colored dye is measured at 505 nm and is proportional to triglycerides concentration in the sample which is estimated as mg/dL [10].

### B. Total cholesterol and HDL-cholesterol

In this estimation, cholesterol esters are hydrolyzed by cholesterol esterase (CE) to give free cholesterol and fatty acids. In subsequent reaction, cholesterol oxidase (CHOD) oxidizes the 3-OH group of free cholesterol to liberate cholest-4-en-3-one and hydrogen peroxide. In

presence of peroxidase (POD), hydrogen peroxide couples with 4-aminoantipyrine (4-AAP) and phenol to produce red quinoneimine dye. Absorbance of colored dye is measured at 505 nm and is proportional to amount of total cholesterol concentration in the sample and is represented as mg/dL [11].

### Calculation:

#### For total cholesterol

Cholesterol concentration (mg/dL) = Absorbance of test / Absorbance of standard X 200

#### For HDL- Cholesterol

HDL-Cholesterol concentration (mg/dL) = Absorbance of test / Absorbance of standard X 50 X 2.

#### For LDL-Cholesterol

The LDL-cholesterol concentration was measured from the formula mentioned below [12];

$$\text{LDL-Cholesterol} = \frac{\text{total cholesterol} - \text{Triglycerides}/5 - \text{HDL-Cholesterol}}$$

**Conversion factor:** Cholesterol concentration in mmol/L = cholesterol concentration in mg/dL X 0.0259.

## 2.6 Antioxidant Activity by Lipid Peroxidation (LPO)

Oxidative stress is associated with peroxidation of cellular lipids, which is determined by the measurement of thiobarbituric acid reacting substance (TBARS). The concentration of LPO products may reflect the degree of oxidative stress. The increased level of TBARS results in increased level of Oxidative Free Radicals, which attacks the polyunsaturated fatty acids in cell membranes and causes LPO. The lipid peroxidation was measured according to the method of Esterbauer and Cheeseman [13].

## 2.7 Statistical Analysis

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

### 3. RESULTS

#### 3.1 Effect of TCE on DOXO-induced Hyperlipidemia in Male Rats

The data from the Table 1 indicated that administration of DOXO at 2.5 mg/kg significantly altered the lipid profile in the male rats. The administration significantly ( $p<0.05$ ) enhanced the levels of total cholesterol, triglycerides and LDL-cholesterol and reduced HDL-cholesterol compared to the control group. Administration of *Terminalia chebula* extract (TCE) along with DOXO showed a dose-dependent alteration in the lipid profile. TCE at 0.25 gm significantly ( $p<0.05$ ) reduced the total cholesterol compared to DOXO. At 0.5 gm, TCE exhibited further reduced ( $p<0.01$ ) in total cholesterol and reversed significantly ( $p<0.05$ ) the triglycerides and LDL-cholesterol levels compared to DOXO group. The highest tested dose of TCE (1 gm/kg) showed further increase in the activity as observed from the turnaround in the activity of total cholesterol ( $p<0.001$ ), triglycerides ( $p<0.01$ ), HDL-cholesterol ( $p<0.05$ ) and LDL-cholesterol ( $p<0.05$ ) compared to the challenge group. Further, TCE tested alone at 1 gm/kg did not alter significantly the lipid profile.

#### 3.2 Effect of TCE on DOXO Altered Lipid Profile in Female Rats

Similar to male rats, DOXO treatment in the female animals also produced significant alteration in the lipid profile compared to the control group. The administration of TCE at 0.5

gm showed significant ( $p<0.05$ ) reduction only in the triglyceride levels, however, TCE at 1 gm demonstrated more reduction in the level of cholesterol ( $p<0.05$ ), triglycerides ( $p<0.01$ ) and LDL-cholesterol ( $p<0.05$ ) compared to DOXO-treated animals. The treatment of TCE at 0.25 gm with DOXO as well as TCE (1 gm/kg) alone did not significantly alter the lipid profile (Table 2).

#### 3.3 Effect of Pre-treatment and Post-treatment of TCE in Male Rats

The study to evaluate the pre- and post-treatment effect of TCE on lipid profile revealed that administration of TCE (0.5 gm/kg) after DOXO (post-treatment) significantly ( $p<0.05$ ) reversed the elevated levels of total cholesterol (TC), triglycerides (TGs) and LDL-cholesterol (LDL-C) compared to the DOXO treated animals. However, the pretreatment of TCE did not show significant variation in the levels of altered lipid profile induced by DOXO (Fig. 1).

#### 3.4 Effect of Pre-treatment and Post-treatment of TCE in Female Rats

The data from female animals are summarized in Fig. 2. Administration of TCE at 0.5 gm/kg after DOXO treatment showed significant ( $p<0.05$ ) reduction in the TGs levels compared to DOXO group. However, other estimations did not show significant variations. Similarly, the pretreatment also did not significantly alter the lipid profile in the DOXO-administered animals.

**Table 1. Effect of *Terminalia chebula* on lipid profile in doxorubicin-treated male rats**

Treatment and dose	Cholesterol (mg/dl)	Triglyceride (mg/dl)	HDL- Cholesterol (mg/dl)	LDL- Cholesterol (mg/dl)
Normal control (Saline 1 ml/kg)	55.46 ± 6.534	103 ± 1.98	17.49 ± 0.76	20.6 ± 0.40
<i>Terminalia chebula</i> (1 g/kg)	52.93 ± 7.905	94.04 ± 1.72	19.09 ± 1.27	16.73 ± 0.59
Doxorubicin (2.5 mg/kg)	115.7 ± 11.65 <sup>b</sup>	315.9 ± 4.73 <sup>b</sup>	13.69 ± 1.00 <sup>a</sup>	63.18 ± 0.95 <sup>a</sup>
DOX 2.5 mg/kg + TCE 0.25 g/kg	102.29 ± 10.35*	316.1 ± 0.52	12.77 ± 0.12	65.18 ± 0.16
DOX 2.5 mg/kg + TCE 0.50 g/kg	88.79 ± 5.75**	276.3 ± 0.91*	14.12 ± 0.35	54.46 ± 0.18*
DOX 2.5 mg/kg + TCE 1.00 g/kg	69.92 ± 10.35***	172.3 ± 2.73**	16.07 ± 0.32*	47.46 ± 1.55*

Values are represented as Mean ± SEM.; n= 6

Statistics: Two-way ANOVA with Bonferroni comparison

<sup>a</sup> $p<0.05$ , <sup>b</sup> $p<0.001$  compared to normal control

\*  $p<0.05$ , \*\* $p<0.01$  \*\*\* $p<0.001$  compared to Doxorubicin treated animals

**Table 2. Effect of *Terminalia chebula* on lipid profile in doxorubicin-treated female rats**

Treatment and dose	Cholesterol (mg/dl)	Triglyceride (mg/dl)	HDL- Cholesterol (mg/dl)	LDL- Cholesterol (mg/dl)
Normal control (Saline 1 ml/kg)	46.22 ± 4.62	86.35 ± 4.6	17.32 ± 0.12	17.27 ± 0.92
<i>Terminalia chebula</i> (1 g/kg)	41.75 ± 5.59	74.71 ± 1.71	19.27 ± 1.27	14.29 ± 0.34
Doxorubicin (2.5 mg/kg)	99.17 ± 8.24 <sup>b</sup>	293.0 ± 3.64 <sup>b</sup>	14.69 ± 1.23 <sup>a</sup>	58.59 ± 0.73 <sup>b</sup>
DOX 2.5 mg/kg + TCE 0.25 g/kg	100.93 ± 7.32	297.4 ± 0.27	14.43 ± 0.34	57.4 ± 0.05
DOX 2.5 mg/kg + TCE 0.50 g/kg	99.92 ± 4.07	267.6 ± 4.74*	14.06 ± 0.37	56.52 ± 1.25
DOX 2.5 mg/kg + TCE 1.00 g/kg	75.28 ± 7.32*	224.8 ± 1.22**	14.28 ± 0.71	46.95 ± 0.24*

Values are represented as Mean ± SEM.; n= 6

Statistics: Two-way ANOVA with Bonferroni comparison.

<sup>a</sup>p<0.05, <sup>b</sup>p<0.001 compared to normal control

\*p<0.05, \*\*p<0.01 compared to Doxorubicin treated animals

### 3.5 Effect of TCE on Serum Lipid Peroxidation

The data for lipid peroxidation indicated that administration of DOXO (2.5 mg/kg) produced significant ( $p<0.001$ ) elevation compared to the control group. Administration of TCE showed a dose dependent reduction in the lipid peroxidation and the maximum inhibition was observed at 1 g ( $p<0.001$ ) compared to the DOXO group. The post treatment of TCE at 0.5 g also showed significant ( $p<0.05$ ) lipid peroxidation lowering effect in the DOXO treated animals. However, pretreatment of TCE did not produced significant alteration in the lipid peroxidation in the test group. Further, when TCE was tested at 1 g in normal animals no significant change in the lipid peroxidation was observed (Fig. 3).

## 4. DISCUSSION

In this study, the effect of *Terminalia chebula* extract (TCE) was evaluated against the doxorubicin (DOXO) induced hyperlipidemia in rats. Separate evaluation was done for male and female rats and the results are summarized in Tables 1, 2 and Figs. 1, 2. The role of TCE on the lipid peroxidation was represented in Fig. 3.

Our observations indicated that DOXO (2.5 mg/kg) significantly ( $p<0.01$ ) altered the lipid profile in the male rats (Table 1). The data from the female rats indicated that though DOXO induced hyperlipidemia similar to male rats but

the effect of TCE in reducing the changes was observed mostly at 1 g/kg dose (Table 2).

DOXO is an anticancer antibiotics and acts by intercalating into DNA double helix. One of the adverse effects of DOXO is alteration of the lipid profile [4]. It was reported in the earlier studies that DOXO administration induces hyperlipidemia in experimental rats. And due to this DOXO is reported to be used as a model for testing the anti-hyperlipidemic activity of test compounds. The mechanism suggested for this is the induction of oxidative stress [14].

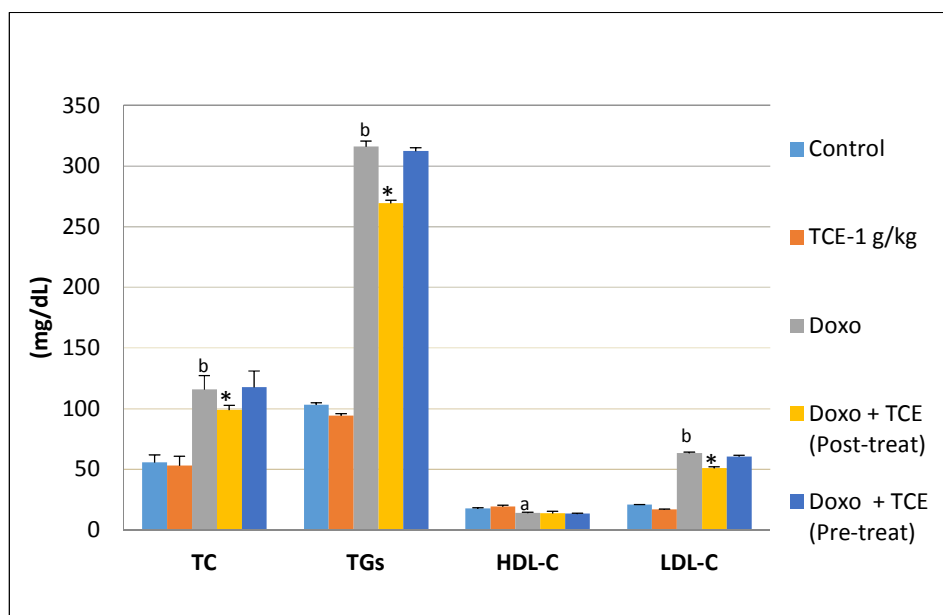
As reported, DOXO may generate reactive oxygen species (ROS) by more than one mechanism. Reduction of DOXO by one electron via mitochondrial reductase may generate anthracycline semiquinone free radicals. Under aerobic conditions, these were reported to be highly unstable and readily reduce molecular oxygen to the ROS superoxide anion and H<sub>2</sub>O<sub>2</sub>. Redox reactions subsequent to interaction of DOXO with iron (III) may generate an iron II-DOXO free radical, capable of reducing molecular oxygen [15].

The oxidative stress reported to elevate the level of malondialdehyde resulting in increase in total cholesterol, triglycerides, LDL-cholesterol and reduced HDL-cholesterol. In our studies also the administration of DOXO induced hyperlipidemia and enhanced the serum lipid peroxidation levels (Tables 1 and 2), suggesting that generation of ROS could be responsible for the alteration of lipid profile [16].

*Terminalia chebula* from ancient times is a vital component of ayurvedic system of medicine. Studies in the past reported that the extract of *Terminalia chebula* possess anti-hyperlipidemic activity [7]. In the present study, we tested three patterns of administration of *Terminalia chebula* extract (TCE). First, TCE was administered simultaneously with DOXO, second, TCE was administered prior to DOXO and in the third TCE was treated after the DOXO administration. These trials were designed to evaluate the role of TCE in reducing the adverse effects of DOXO. Our observations indicated that simultaneous administration of TCE showed a dose-dependent inhibition in DOXO-induced hyperlipidemia. A significant response of TCE was observed at 0.5 and 1 g/kg dose in male rats (Table 1). Furthermore, when TCE was tested in female rats all the tested doses did not alter significantly the HDL-cholesterol in DOXO-treated animals, though other lipid parameters showed significant reduction (Table 2). In the pre and post-treatment analysis, our data indicated that TCE at 0.5 g/kg was found to be effectively in reducing the levels of TC, TGs and LDL-C in the post-treatment schedule, however, the pre-treatment did achieve significant variation in the altered lipid profile (Fig. 1). The results from the female group indicated that only post treatment

produced significant reduced in TGs levels. Other lipid levels did not change significantly and also the pre-treatment had no-significant activity on the DOXO-altered hyperlipidemia (Fig. 2).

Several studies in the past reported that herbal medicines containing alkaloids, phytosterols, saponins, tannins, ellagic acid, gallic acid, chebulinic acid, chebugalic acid and corilagin produces a significant lipid lowering activity [17]. High amount of saponins, phytosterols, chebulinic acid and corilagin was also reported to be present in *Terminalia chebula* and thus could be responsible for the hypolipidemic effect in the present study [7,18]. Moreover, the antioxidant study also indicated that administration of TCE reduced the serum lipid peroxidation levels in the animals (Fig. 3). Together, these properties of TCE might have contributed in the reduction of hyperlipidemic activity of DOXO. The insignificant alterations in the level of HDL-cholesterol in female rats after the administration of TCE suggests that the genetic and hormonal variations might have contributed in the pharmacokinetic and pharmacodynamics differences of the drugs, since earlier studies suggests that these disparities are responsible for changes in drug activity in male and female

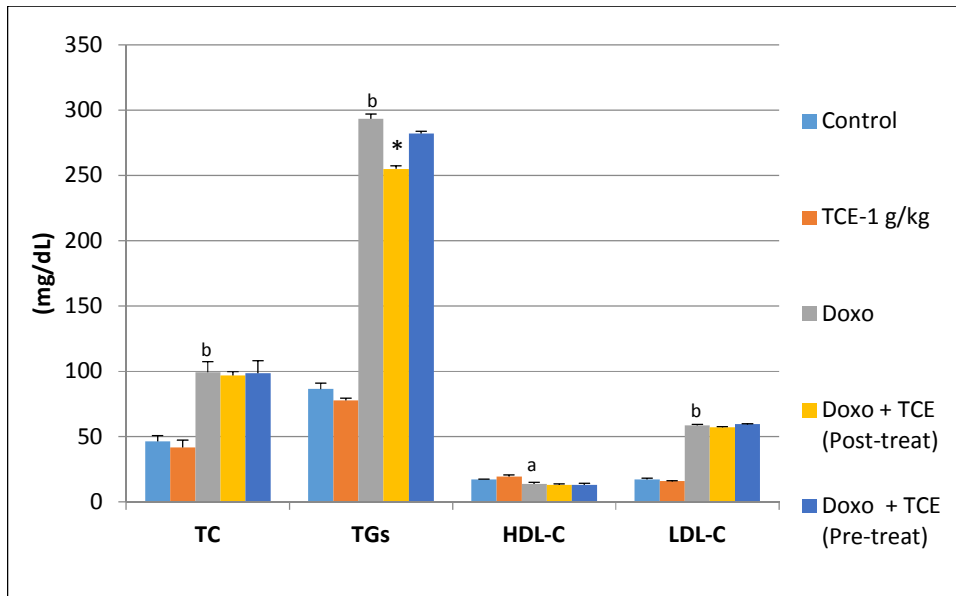


**Fig. 1. Effect of pre-treatment and post-treatment of TCE (0.5 g) on Doxo-hyperlipidemia in male rats**

Values are represented as Mean ± SEM.; n= 6

Statistics: Two-way ANOVA with Bonferroni comparison

<sup>a</sup>p<0.05, <sup>b</sup>p<0.001 compared to normal control. \* p<0.05 compared to Doxorubicin treated animals

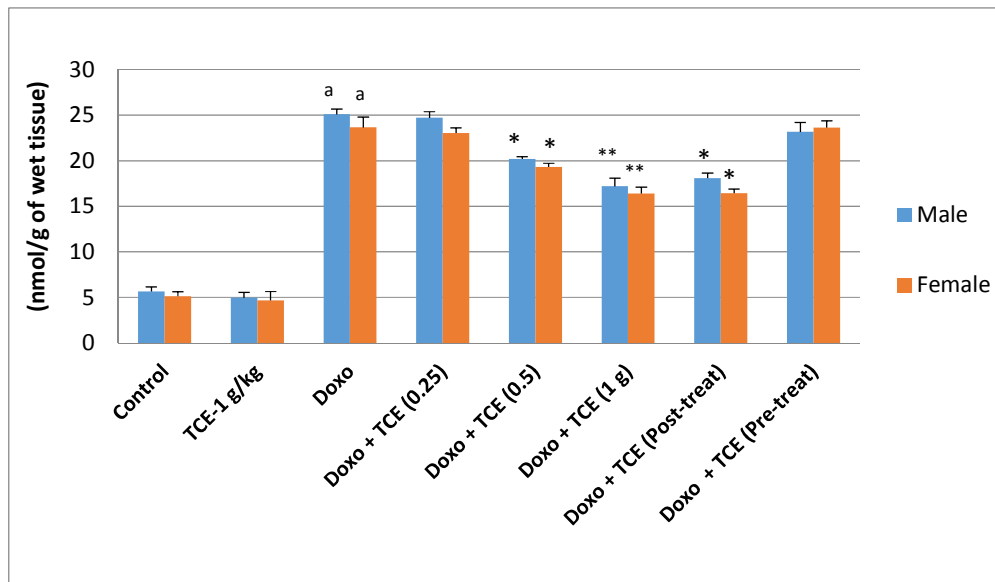


**Fig. 2. Effect of pre- and post-treatment of TCE (0.5 g) on Doxo-hyperlipidemia in female rats**

Values are represented as Mean  $\pm$  SEM.; n = 6

Statistics: Two-way ANOVA with Bonferroni comparison

<sup>a</sup>p<0.05, <sup>b</sup>p<0.001 compared to normal control. \* p<0.05 compared to Doxorubicin treated animals



**Fig. 3. Effect of TCE on lipid peroxidation**

Values are represented as Mean  $\pm$  SEM.; n = 6

Statistics: 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

species [19]. Similar mechanisms have also been suggested for the variation in the levels of lipids between genders [20], since the data from this study indicated a significant difference ( $p<0.01$ ) when comparison was done for the

levels of triglyceride and LDL-cholesterol between male and female rats (Tables 1 and 2). Further research might provide more details about the precise mechanism for the differences in the effects of TCE.

## 5. CONCLUSION

The present study indicated that *Terminalia chebula* extract decreased the doxorubicin induced hyperlipidemia in rats. Simultaneous as well as post-DOXO administration of the extract might benefit in reducing hyperlipidemia. The activity of the *Terminalia chebula* could be related to the phytochemical constituents present in the extract and also due to the lipid peroxidation lowering property. However, the prior administration of TCE has showed no significant lipid lowering activity at the tested dose.

## CONSENT

It is not applicable.

## ETHICAL APPROVAL

The experiments were conducted in CPCSEA (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.

## COMPETING INTERESTS

Authors have declared that no competing interests exist.

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