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Research Article

EVALUATION OF HEPATOPROTECTIVE ACTIVITY OF *DRACAENA TERNIFLORA* ROXB. AGAINST ETHANOL INDUCED HEPATIC INJURY IN *WISTAR* ALBINO RATS

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ABSTRACT

Objectives: The objectives of the study were to investigate hepatoprotective activity of ethanolic root extract of *Dracaena terniflora Roxb*. (DTR-E) in alcohol-induced hepatotoxicity in rats.

Methods: Hepatotoxicity was induced in albino Wistar rats by oral administration of 40% ethanol (2 mL/100 g body weight). DTR-E root extract was administered at a dose level of 100 mg/kg and 200 mg/kg orally for 21 days. On the 22nd day blood was taken by puncturing retro orbital plexus and used for the estimation of biochemical parameters such as alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), total bilirubin, creatinine, urea, triglycerides, total cholesterol, albumin, and total protein. Animals were sacrificed by cervical dislocation and liver was dissected out and histopathological analysis of liver and kidney was carried out.

Results: Obtained results revealed that administration of ethanol caused a significant increase in liver weight, plasma ALT, AST, ALP, bilirubin creatinine, urea, triglycerides,and total cholesterol compared to the control group, while total protein and albumin concentration are significantly declined which were effectively prevented by the DTR-E extract. The histopathological observations supported the biochemical evidence of hepatoprotection.

Conclusions: The findings suggest that DTR-E root extract protects the liver cell from ethanol induced liver damages due to its antioxidative effect on hepatocytes. The results of the present investigation indicated that roots of *D. terniflora* Roxb. possesses significant hepatoprotective activity.

Keywords: Hepatoprotective, Ethanol, *Dracaena terniflora* Roxb. Silymarin, *In vivo.*

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INTRODUCTION

Liver disease is leading as one of the most severe health issues. Herbal drugs play a key role in the management of hepatic disorders. In the absence of reliable liver hepatoprotective drugs in modern medicine, a number of medicinal plants and their formulations are consumed to cure hepatic disorders in traditional systems of medicine [1]. The increasing use of herbal medicines reflects their perceived effectiveness in the treatment and prevention of disease, and the belief that these treatments are safe because they are "natural." Researchers have utilized different scientific methods to evaluate the effectiveness of herbs for the cure of liver ailments and in many cases the mechanisms and modes of action of these herbs, as well as their therapeutic effectiveness, have been set [2]. In spite of the availability of more than 300 preparations for the treatment of jaundice and chronic liver diseases in Indian systems of medicine, only few medicinal herbs have been scientifically elucidated though adhering to the internationally acceptable scientific protocols [3]. To obtain the satisfactory herbal drugs for treating severe liver diseases, the medicinal plants must be evaluated systematically for properties such as antiviral activity (Hepatitis B, Hepatitis C, etc.), antihepatotoxicity activity (antioxidants and others), stimulation of liver regeneration, and choleretic activity [4].

Dracaena terniflora Roxb. (*Pleomele terniflora* Roxb.) is a traditional medicinal herb; also known as Dwarf dracaena or Wild dracaena belongs to the family *Liliaceae. D. terniflora* Roxb. is a low decumbent slender perennial shrub usually grows found in evergreen and semi evergreen forests in India and South-East Asia. The various parts of the plant are used for diverse health ailments in traditional and folklore remedies. The decoction of the roots of this plant is used for treating spermaturia [5]. The fresh juice of this plant is used for the treatment of diabetes by the Kurunarippullu tribes of Wayanad, Kerala [6]. Roots are taken internally for the cure of jaundice after boiling with rice. Fruits boiled with coconut oil are applied on the forehead against headache [7]. Roots of this plant is used for the treatment of various liver disorders especially jaundice by the various tribal communities of Kerala [8]. Traditionally, the root and fruit are used in bed sores [9].

In our earlier studies, it has been reported that the ethanolic extract of roots of *D. terniflora* Roxb. (DTR-E) possesses *in vitro* antioxidant activity and has also revealed the presence of alkaloids, flavonoids, phenols, saponins, steroids, tannins, terpenoids, and absence of anthocyanins and glycosides [10]. *In vitro* antidiabetic and hepatoprotective activities have also been scientifically studied recently in the roots of this plant [11,12].

The present study evaluated the proposed folklore claim of hepatoprotective activity of the DTR-E against ethanol-induced liver damage in *Wistar* albino rats.

METHODS

Materials

The whole plant of *D. terniflora* Roxb. was collected from April to June 2017 from the semi forest regions of Wayanad, Kerala, India, and identified by Dr. Sr. Tessy Joseph, H.O.D Department of Botany, Nirmala College, Muvattupuzha, Kerala, India, where a herbarium specimen was deposited (Voucher number: NCH/2017/538). Fresh plant materials were washed thoroughly in running tap water to remove adhering impurities, shade dried to constant weight. The roots and aerial parts were separated. Roots were stored in a tightly closed container after powdering and sieving (40-mesh size). It was stored in a tightly closed container. All the drugs, chemicals, and reagents used for biochemical estimation were purchased from Span Diagnostics Ltd. India. Male and

Table 1: *In vivo* hepatoprotective experimental design

Groups	Category	Treatment
Group I	Normal control	Distilled water (5 mL/kg p.o.) for 21 days once daily
Group II	Negative control (toxic control)	40% ethanol v/v (2.0 mL/l00 g body weight, p.o.) once daily for 21 days
Group III	Standard (silymarin)	40% ethanol v/v (2.0 mL/l00 g body weight, p.o.) and standard drug silymarin (25 mg/kg p.o.) for 21 days once daily
Group IV	Low dose (100 mg/kg)	40% ethanol v/v (2.0 mL/l00 g body weight, p.o.) and DTR-E root extract for 21 days once daily
Group V	High dose (200 mg/kg)	40% ethanol v/v (2.0 mL/l00 g body weight, p.o.) and DTR-E root extract for 21 days once daily

female *Wistar* albino rats, weighing about 150–200 g, were procured and maintained under standard laboratory condition in Arulmigu Kalasalingam College of Pharmacy, Krishnan Koil, Tamil Nadu. Statistical analysis was performed using SPSS 11.0 software package (SPSS, Tokyo, Japan).

Preparation of extract

Dried root powder was extracted with ethanol using Soxhlet apparatus. Exhaustive extraction was applied for 10 h to safeguard complete extraction procedures. The extract was then recovered from the solvent through evaporation in a rotary evaporator at 60°C and final drying was done by keeping the extract in desiccator for an hour to collect some reddish-brown colored semisolid sticky mass. The percentage yield of the ethanolic extract was 6.31%.

Acute oral toxicity study

Healthy *Wistar* albino female rats weighing 150–200 g maintained under standard laboratory conditions were used for acute oral toxicity test according to Organization for Economic Co-operation and Development guidelines 423 [13,14]. Albino rats were kept in polypropylene cages in animal house under standard environmental conditions. The animals were fasted for 16 h before experiment but allowed free access to water. The animals will be maintained under standard condition of temperature 23±2°C, relative humidity 55±10%, and 12 h dark/light cycle with access to standard dry pellet diet and water *ad libitum*. Control of temperature and humidity prevents variation due to changes in climatic conditions. The animals will be acclimatized to the study environment for 7 days before the experimental sessions and all the procedures will be strictly followed in accordance with the regulations of CPCSEA. The experimental procedures were approved by the Institutional Animal Ethics Committee (IAEC), Arulmigu Kalasalingam College of Pharmacy, Krishnan Koil, Tamil Nadu (AKCP/IAEC/21/2019-2020).

Experimental design

Induction of experimental hepatotoxicity

Rats were divided into five groups each containing six rats and were treated with 40% ethanol (2 mL/100 g body weight orally) for 21 days once daily to induce toxicity study and the effect of ethanolic root extract was evaluated using silymarin which was used as a standard drug [13,15-19].

Collection of blood samples

Blood samples were collected by puncturing retro orbital plexus on 22nd day done under anesthesia using halothane into dry clean bottles and allowed to coagulate for 30 min at room temperature. Serum was separated by centrifugation (2500 rpm for 15 min), stored at -20°C and EDTA was used as an anticoagulant for hematological parameters.

Biochemical estimation

The biochemical parameters including serum enzymes such as aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase (ALP), along with total bilirubin, creatinine, urea, triglycerides, total cholesterol, albumin, and total protein content were assayed using analytical kits. To evaluate the liver enzyme profiles, enzyme-linked immunosorbent assay kits were utilized.

The serum AST was estimated by the method of Reitman and Frankel (1957) using AST test kit (Span Diagnostics Ltd) [20]. The serum ALT was estimated by the method of Reitman and Frankel (1957) using ALT test kit (Span Diagnostics Ltd.) [20]. ALP activity was estimated by the method of Kind and King (1954) using ALP test kit (Span Diagnostics Ltd.) [21]. Serum urea was estimated using the diagnostic kit based on the method of Fawcett and Scott (1960) [22]. Serum creatinine was estimated using the diagnostic kit based on the method of Tietz (1987) using Jaffe's (1886) color reaction [23]. Estimation of total bilirubin was followed by modified DMSO method (Malloy and Evelyn, 1936) [24]. Triglycerides were estimated by the method of Foster and Dunn (1973) [25]. In the present study, the serum cholesterol is estimated by the method of Allain *et al*., 1974 [26]. Estimation of total protein (Lowry *et al*., 1951) [27]. The serum albumin was estimated by the method given by Corcoran and Durban, 1977 using albumin test kit (Span Diagnostics Ltd.) [28].

Histopathological examination

At the end of the experiment (day 22), all rats were sacrificed by cervical dislocation method and the liver and kidney were excised out and fixed in formalin (10%). Five microns thick sections were prepared using microtome. The tissues were dissected out and fixed in 10% formalin, dehydrated in gradual ethanol (50–100%), cleared in xylene, and embedded in paraffin. Sections were prepared and then stained with hematoxylin and eosin dye for photo microscopic observation, including cell necrosis, fatty change, hyaline regeneration, and ballooning degeneration (Luna, 1968) [29].

Statistical analysis

Results were expressed as the means±standard deviation. Significant difference between the means of the six groups was statistically analyzed by analysis of variance and Duncan's Multiple Range Test. The significance levels were set at $p<0.05$ for all the tests.

RESULTS AND DISCUSSION

Acute toxicity

The results of acute toxicity study revealed that LD_{50} values of plant were high and apparently showed the safety of the extract. As represented in Table 1. The rats which were orally administered with DTR -E root extract did not show any symptoms of toxicity or mortality, particularly when the dose was increased to 2000 mg/kg body weight. Administration of DTR-E root extract did not make any change in the autonomic or behavioral response in rats. The 0% mortality was recorded even at 2000 mg/kg and suggested the LD_{50} value as 2000 mg/kg. Hence, therapeutic dose was calculated as 1/20th, 100 mg/kg as the low dose, 1/10th, 200 mg/kg as the high dose for the purpose of hepatoprotective investigations of plant extract.

The effect of DTR-E extract on average liver weight changes in *Wistar* albino rats

Results presented in Table 2 and Fig. 1 represents the effects of DTR-E and standard drug Silymarin on average liver weight in normal and ethanol-induced hepatotoxic rats. Results showed an increase in average liver weight in the ethanol induced hepatotoxic group of rats. The administration of DTR -E extract attenuated the elevated liver weight and silymarin treated group restored liver weight to almost normal.

Effect of DTR-E on liver enzymes and other parameters in ethanol-induced hepatotoxicity in *Wistar* rats

Results presented in Table 3 and Fig 2 exhibited the effect of DTR-E root extract on hepatic marker enzymes in the serum from normal

and ethanol-induced hepatotoxic rats. The hepatotoxic control group showed increased levels of ALT (159.36±4.50), AST (201.56±4.62), and ALP (480.64±10.74) in Group II rats. Administration of DTR-E extract showed considerable decrement in AST, ALP, and ALP in Groups IV and V group rats. Administration of the lower dose (100 mg/kg) showed ALT (122.54±4.18), AST (128.64±4.76), and ALP (308.45±1.68) in Group IV rats. Administration of higher dose (200 mg/kg) showed ALT (70.78±3.26), AST (98.23±4.58), and ALP (232.68±9.22) in Group V rats. The administration of DTR-E root extract diminished the elevated levels of the hepatic marker enzymes and silymarin restored enzyme activities to normal values. Thus, the toxic effect of ethanol was significantly controlled in the animals treated with DTR-E extract.

Table 4 and Fig. 3 summarized the effect of DTR-E root extract on creatinine, urea, and total bilirubin in the serum in ethanol-induced hepatotoxic rats. The hepatotoxic control group (Group II) showed increased the levels of creatinine, urea, and total bilirubin when compared to a control group of rats (Group I). Treatment with DTR-E roots extract showed significant reduction in the elevated levels of creatinine, urea, and total bilirubin in toxicity induced rats and silymarin restored creatinine, urea, and total bilirubin to normal value.

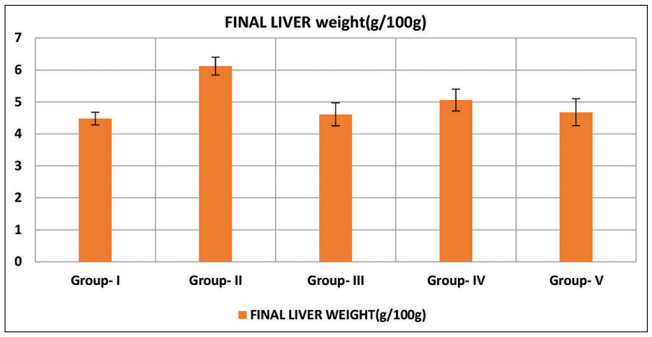


Fig. 1: The effect of DTR-E root extract on average liver weight changes in rats

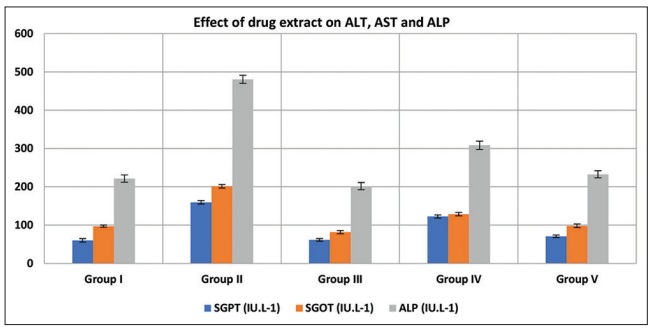


Fig. 2: Effect of plant extract (DTR-E) on liver enzymes (ALT, AST, and ALP) by ethanol-induced hepatotoxicity in *Wistar* albino rats

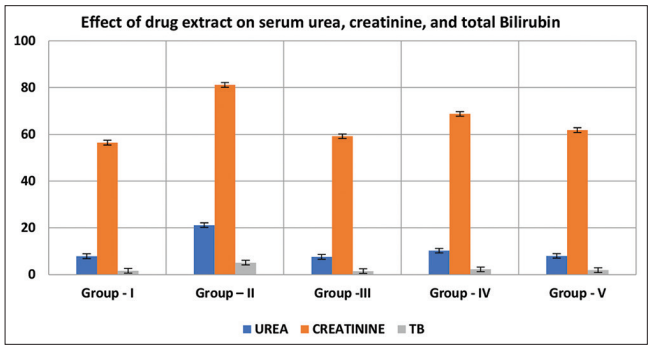


Fig. 3: Effects of the plant extract (DTR-E) on serum urea, creatinine, and total bilirubin in alcohol treated rats

Table 5 and Fig. 4 displayed the effect of DTR-E root extract on TG and TC in the serum of ethanol-induced hepatotoxic rats. The hepatotoxic (negative control) group (Group II) showed increased the level of TG as 91.35±3.88 and TC as 210.46±3.58 while comparing with that of Group I rats. Oral administration of DTR-E extracts showed considerable reduction TG and TC levels in Groups IV and V rats. Oral administration of the lower dose of DTR-E root extract showed considerable reduction in TG and TC levels in Group IV rats as 70.24±3.18 and 122.58±3.84 while comparing with Group II toxic group. Oral administration of higher dose of DTR-E root extract showed marked reduction in the level of TG and TC in Group V rats as 61.14±3.32 and 99.38±2.78. Silymarin treated Group III indicated significant reduction in the level of TG and TC to almost normal.

Table 2: Effect of *Dracaena terniflora* Roxb. extract on average liver weight changes in *Wistar* albino rats

Treatment	Final liver weight (g/100 g)
Group-I	$4.48\pm0.20^{b*}$
Group-II	$6.12\pm0.28^{a*}$
Group-III	$4.61\pm0.36^{a*,b*}$
Group-IV	$5.06\pm0.34^{a**,b*}$
Group-V	$4.68\pm0.42^{a*,b*}$

p: *<0.001, **<0.05, [a]Group I matchup with Groups II, III, IV, V, [b]Group II matchup with Groups III, IV, V. Values are expressed as mean±SE (n=6 rats). SE: Standard error

Table 3: Effect of the ethanolic extract of roots of *Dracaena terniflora* Roxb. on liver enzymes (ALT, AST and ALP) by ethanol-induced hepatotoxicity in *Wistar* albino rats

Treatment	ALT (IU L – 1)	AST (IU L – 1)	ALP (IU L – 1)
Group I	$60.23\pm43.54^{b*}$	$97.03\pm2.74^{b*}$	$221.52\pm9.65^{b*}$
Group II	$159.36\pm4.50^{a*}$	$201.56\pm4.62^{a*}$	$480.64\pm10.74^{a*}$
Group III	$61.32\pm3.46^{a*,b*}$	$81.72\pm4.23^{a*,b*}$	$201.84\pm9.36^{a*,b*}$
Group IV	$122.54\pm4.18^{a**,b**}$	$128.64\pm4.76^{a*,b**}$	$308.45\pm10.68^{a**,b*}$
Group V	$70.78\pm3.26^{a*,b*}$	$98.23\pm4.58^{a**,b*}$	$232.68\pm9.22^{a*,b*}$

p: *<0.001, **<0.05, [a]Group I matchup with Groups II, III, IV, V, [b]Group II matchup with Groups III, IV, V. Values are expressed as mean±SE (n=6 rats). ALT: Alanine aminotransferase, AST: Aspartate aminotransferase, ALP: Alkaline phosphatase, SE: Standard error

Table 4: Effects of plant extract (*Dracaena terniflora* Roxb.) on serum urea, creatinine and TB in alcohol treated rats

Treatment	Urea ($mmoL^{-1}$)	Creatinine ($mmoL^{-1}$)	TB (mg/dL)
Group-I	$7.84\pm0.78^{b*}$	$56.42\pm4.12^{b*}$	$1.62\pm0.03^{b*}$
Group-II	$21.16\pm1.28^{a*}$	$81.15\pm6.58^{a*}$	$5.10\pm0.06^{a*}$
Group-III	$7.58\pm1.10^{a*,b*}$	$59.18\pm6.23^{a*,b*}$	$1.48\pm0.05^{a*,b*}$
Group-IV	$10.24\pm1.16^{a*,b*}$	$68.76\pm5.38^{a*,b*}$	$2.25\pm0.04^{a**,b*}$
Group-V	$7.98\pm1.08^{a**,b*}$	$61.84\pm5.42^{a**,b*}$	$1.90\pm0.06^{a*,b*}$

p: *<0.001, **<0.05, [a]Group I matchup with Groups II, III, IV, V, [b]Group II matchup with Groups III, IV, V. Values are mean±SE of 6 rats. NS: Non-significant, SE: Standard error, TB: Total bilirubin

Table 5: Effects of plant extract on serum TG and TC in ethanol treated rats

Treatment	TG (mg/dL)	TC (mg/dL)
Group-I	$58.43\pm3.06^{b*}$	$96.24\pm1.92^{b*}$
Group-II	$91.35\pm3.88^{a*}$	$210.46\pm3.58^{a*}$
Group-III	$57.18\pm3.64^{a*,b*}$	$94.85\pm2.10^{a*,b*}$
Group-IV	$70.24\pm3.18^{a*,b**}$	$122.58\pm3.84^{a*,b**}$
Group-V	$61.14\pm3.32^{a**,b*}$	$99.38\pm2.78^{a*,b*}$

p: *<0.001, **<0.05, [a]Group I matchup with Groups II, III, IV, V, [b]Group II matchup with Groups III, IV, V. Values are expressed as mean±SE (n=6 rats). SE: Standard error, TG: Triglycerides, TC: Total cholesterol

Effect of DTR-E root extract on total protein and albumin in the serum from normal and ethanol-induced hepatotoxic rats is depicted in Table 6 and Fig. 5. The hepatotoxic control group showed a reduction of TP as 5.70±1.28 and albumin as 5.31±1.10. Oral administration of DTR-E extract showed considerable increase in TP and ALB levels in Groups IV and V rats. Oral administration of the lower dose of DTR-E extract showed a reasonable increase in TP and albumin levels in Group IV rats as 7.18±1.14 and 6.74±1.16. Oral administration of high dose of DTR-E root extract almost restored the level of TP and in Group V rats toward normal. Silymarin treated rats have significantly elevated the level of TP and albumin as compared to normal control rats.

Histopathological results of liver and kidney

The histopathological studies revealed the actual changes which occurred in the cellular structure of rat liver and kidney after ethanol intoxication. Liver segment of normal Group I control rats exhibited normal liver lobular architecture with prominent nucleus and well brought out central vein and nucleolus. Toxic control alcohol treated rat liver (Group II) showed severe toxicity with congested blood vessels with inflammatory cell collection and endothelial cell swelling. Low dose treated rats (Group IV) presented only moderate inflammation. High dose treated rats (Group V) showed only a mild inflammatory cell around portal tract. Rats treated with silymarin (Group III) showed marked regenerative property against ethanol toxication displayed presence of normal cellular boundaries and absence of necrosis.

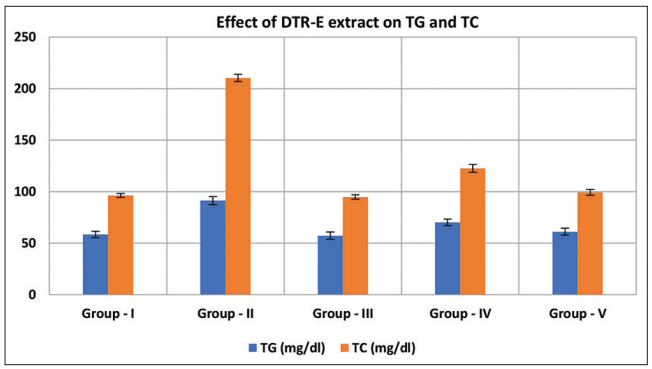


Fig. 4: Effects of the plant extract on serum TG and TC in the ethanol treated rats

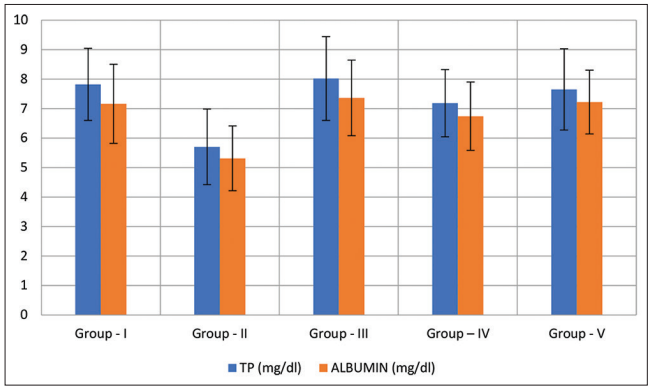
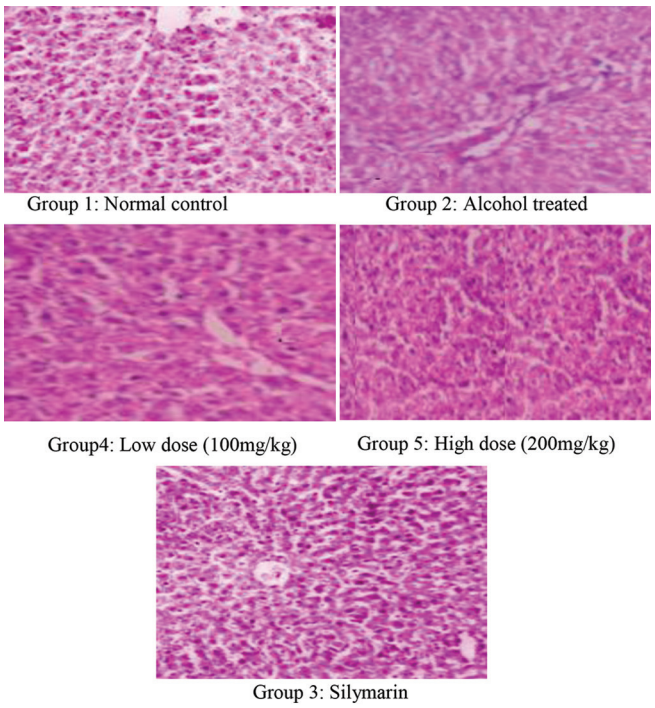


Fig. 5: Effects of the plant extract on serum TP and ALB in the alcohol treated rats

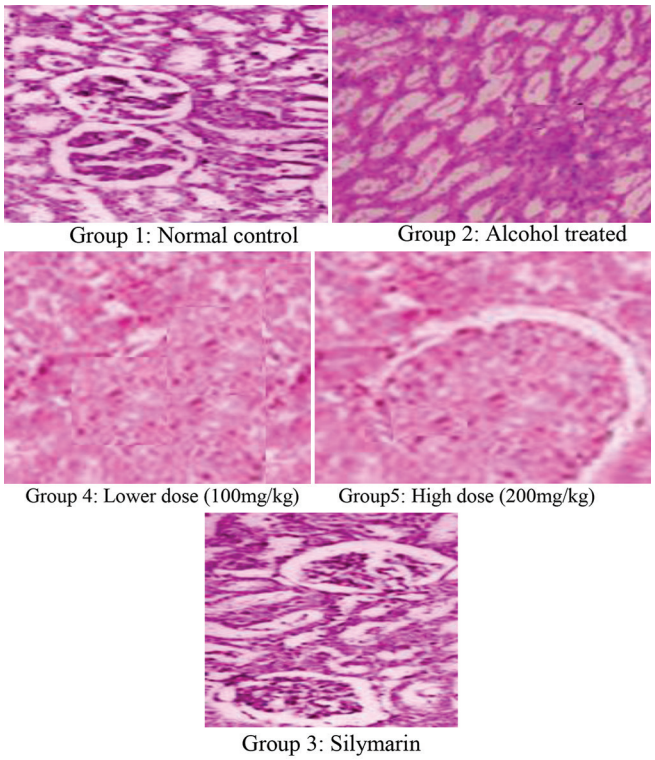
Table 6: Effects of plant extract on serum TP and ALB in alcohol treated rats

Treatment	TP (mg/dL)	ALB (mg/dL)
Group-I	7.82±1.22[b*]	7.16±1.34[b*]
Group-II	5.70±1.28[a*]	5.31±1.10[a*]
Group-III	8.02±1.42[a*,b*]	7.36±1.28[a*,b*]
Group-IV	7.18±1.14[a*,b*]	6.74±1.16[a**,b*]
Group-V	7.65±1.38[a*,b*]	7.22±1.08[a*,b*]

p: *<0.001, **<0.05, [a]Group I matchup with Groups II, III, IV, V, [b]Group II matchup with Groups III, IV, V. Values are mean±SE of 6 rats.
NS: Non-significant, SE: Standard error, ALB: Albumin, TP: Total protein



Histological studies in kidney tissue showed dilated tubules and cloudy swelling of tubules in alcohol administration rats (Group II). The changes were markedly reduced and almost near normal appearance of kidney were observed in rats treated with high dose (200 mg/kg) and alcohol (Group V). Control rats treated group showed the normal appearance of kidney without any histological alterations.



CONCLUSION

The results of the present investigation carried out on *D. terniflora* Roxb. clearly designated the significant hepatoprotective activity of this folklore medicinal plant which could be due to their free radical scavenging and antioxidant activities, resulting from the presence of some phytochemicals including polyphenols, flavonoids, and alkaloids. It substantiates the traditional claims about the use of this plant in the treatment of various liver disorders. These findings show the prophylactic and curative efficacy of *D. terniflora* Roxb.in maintaining the functional status of hepatocytes. Considering the favorable results obtained, further research work may be carried out to isolate, identify, characterize, and standardize the phytoconstituents and evaluating the hepatoprotective effects of the isolated constituents. Furthermore, the exact phytoconstituents and their mechanism of hepatoprotection should also be studied.

AUTHORS' CONTRIBUTION

Dr. Kavitha Vasudevan: First author (Research Scholar)
Dr. Sanilkumar R: Research Guide
Dr. Sabu M C: Research Co-Guide

COMPETING INTERESTS

The authors declare that there is no conflict of interest.

AUTHORS FUNDING

None.

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