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Original Article

Hepatoprotective Potential of *Trichosanthes dioica* Roxb in Hepatotoxicity Induced by Simvastatin and its Consequences on Biochemical and Haematological Indices

Ramesh Kumar Gupta[1,2]*, Sudhansu Ranjan Swain[3], Jagannath Sahoo[4], Amresh Gupta[5], Sachin Chaudhary[6]

ABSTRACT

Objective: To evaluate hepatoprotective activity along with hematological and defensive recital of *Trichosanthes dioica* Roxb against simvastatin induced hepatotoxicity in experimental rodents. **Methods:** In the present study, *in- vivo* hepatoprotective effect of 50% methanolic fruit extract of *Trichosanthes dioica* Roxb (TME 200 and 400 mg/kg body weight) was evaluated using experimental model, simvastatin (20 mg/kg, *p.o.),* induced hepatotoxicity in experimental animals. The hepatoprotective activity was estimatedby interpreting using various biochemical parameters like SGOT, SGPT, ALP, total bilirubin, total protein and albumin along with the haematological and histopathological studies. **Results:** The treatment with TME significantly ($P<0.05$-$P<0.001$) and dose-dependently reversed simvastatin induced elevation in serum level ofSGOT, SGPT, ALP, total bilirubin and restored the total protein and albumin level. Furthermore, TME also signify the blood parameters at dose of 1000 and 2000 mg/kg and restored the body defense mechanism. The histological examination revealed that TME at dose of 200 mg/kg showed regeneration of hepatocytes around central vein with near normal liver architecture. **Conclusion:** The results of this study exhibited liver protective effect of *Trichosanthes dioica* Roxb against simvastatin induced liver injury and there by scientifically support its traditional use.

Key words: Hepatocytes, Hepatotoxicity, Liver, Simvastatin, *Trichosanthes dioica*.

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INTRODUCTION

Trichosanthes dioica Roxb, commonly known as *parwal*, belongs to cucurbitaceae family and is an annual or perennial herb distributed throughout India. Out of 20 species in India, two are cultivated as vegetable (*T. anguina* and *T. dioica).* In Charaka Samhita, leaves and fruits are enlisted for treatment of alcoholism and jaundice. In Ayurveda, leaves are utilized as antipyretic, diuretic, cardiotonic, laxative, antiulcer. *T. dioica* accomodate numerous chemical constituents like vitamin A, saponins, tannins, alkaloids, mixture of novel peptides, proteins and vitamin C.[1,2] Thevarious scientific research revealed that *T. dioica* exhibited anti-diabetic,[3] anti-hypercholesteraemic,[4] hepatoprotective,[5] anti-ulcer,[6] immunomodulatory,[7] antimicrobial,[8] anti-oxidant,[9] anti-diarrheal,[10] nephroprotective,[11] and wound healing activity.[12]

HMG CoA reductase inhibitors (Simvastatin) are effective in reducing cardiovascular mortality and are widely prescribed around the globe. More than 145 million patients were prescribed with statins in United States in 2005. The use of statins is increasing day by day, although liver toxicity has been a concern since their initial introduction.[13] No scientific results are available affirming hepatoprotective potential of *Trichosanthes dioica* Roxb against hepatotoxicity induced by simvastatin. Hence, present investigation was designed to demonstrate hepatoprotective activity of *Trichosanthes dioica* Roxb against simvastatin induced liver toxicity.

MATERIALS AND METHODS

Drugs and Chemicals

Simvastatin (Merck Pharmaceutical, India). All chemicals used were of analytical grade and procured from Sigma Chemicals Co., USA and Qualigens fine chemicals, Mumbai, India.

Collection and authentication of plant

Fresh and matured fruits of *T. dioica* were purchased from local market of Lucknow, India in August 2016. The plant material was identified and authenticated by National Botanical Research Institute, Lucknow, India.

Extraction of plant material

The fruits of *T. dioica* were dried and powdered. The powdered plant material was macerated with petroleum ether; the marc was exhaustively extracted with of 50% methanol for three days. The extract was dried by rotator evaporator (IKA, Germany) under reduced pressure and procured in

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desiccator. The % yield was discovered to be 0.75%. 1% Tween-80 was used to prepare extract suspension of desirable concentration needed for pharmacological studies.

Phytochemical investigation

The methanolic extract of *T. dioica* fruits were subjected to preliminary phytochemical screening for detecting the presence or absence of active phytochemical constituents.[14,15]

Animals

Wistar rats weighing (150-170 g) of either sex were procured from Animal house of College of Pharmacy, Shri Ram Murti Smarak College of Engineering and Technology, Bareilly, India. They were kept in departmental animal house in well cross ventilated room at 22±2˚C with light and dark cycles of 12 h for 1 week before and during the experiments. The experimental protocols were approved by Institutional Animal Ethical Committee, India (Reg. No. 715/02/CPCSEA).

Acute toxicity study

Acute toxicity study was performed according to OECD guidelines 423. Albino mice (20-25 g) were divided into five groups with 5 mice in each. Group-I numbered as control received distilled water orally. Group-II, III, IV, and V were administered *T. dioica* extract at a dose of 5, 50, 300, 2000 mg/kg, orally, respectively. The animals were noticed for toxicity sign or mortality every 24 h, daily for 2 weeks.[16]

Experimental design

Wistar rats were divided into five different groups, each group having 6 rats. Group I received distilled water only for 30 days. Group II rats charged with simvastatin (20 mg/kg, *p.o.)* alone for 30 days orally. Group III and IV rats received simvastatin along with *T. dioica* fruits extracts(200 mg/kg and 400 mg/kg, *p.o.* respectively) for 30 day and Group V rats received simvastatin along with silymarin (20mg/kg,*p.o.*) for 30 days. On the 31thday, blood samples were collected, and all the animals were sacrificed by cervical dislocation under mild ether anesthesia and liver sample were harvested, rinsed in saline and stored at -80˚C for further biochemical analysis.[17]

Evaluation of liver protective activity

The collected blood was allowed to clot and serum was separated by centrifugation in a refrigerated tabletop centrifuge at 2500 rpm for 15 min and the biochemical parameters like serum enzymes: Serum glutamic oxaloacetic transaminase (SGOT, U/L), serum glutamic-pyruvic transaminase (SGPT, U/L),[18] alkaline phosphatase (ALP, U/L),[19] total bilirubin (mg/dL),[20] total protein and albumin were evaluated.[21,22]

Evaluation of hematological parameter

Red blood cell (RBC) count, haemoglobin (Hb), white blood cell (WBC) count, platelet (PLT) and lymphocytes were determined by the fully automated hematology analyzer (XP 100 Hematology Analyzer, Transasia Bio-Medicals Ltd., India).

Histopathological studies

For histopathological inspection, the liver tissues were affixed with 10% phosphate buffered neutral formalin, dehydrated in graded (50-100%) alcohol and embedded in paraffin. fine sections (5 µM) were cut and stained with routine hematoxylin and eosin stain for photo microscopic analysis. All the slides were studied under a light microscope for any histological destruction and protection.

Statistical analysis

The statistical comparison between the groups were made by One Way Analysis of Variance (ANOVA) and followed by Student-Newman-Keuls test. The value $p<0.05$ was considered statistically using, Graph Pad Prism 5.03 Software. The values were represented as mean ± SEM for six rats.

RESULTS

Phytochemical screening

Phytochemical screening showed the presence of tannins, alkaloids, carbohydrates, flavonoids, glycosides and steroids as documented in Table 1.

Acute toxicological outcome

The methanolic extract of *T. dioica* at doses of 200 and 400 mg/kg body weight does not produce any toxic outcome. Therefore, these doses were selected for hepatoprotective studies.

Effect of TME on serum hepatic parameters

The outcome of *T. dioica* fruits extract dose was investigated on liver serum markers like SGOT, SGPT, ALP, bilirubin (BLB), total protein (TP) and albumin (ALB) level. Hepatic abrasion due to dose of simvastatin generate significant elevation in marker enzymes as SGOT by 336.5%, SGPT by 135.7%, ALP by 144%, BLB by 39%, and demotion in level of TP by 48.3% and ALB by 32.5% when compared to control (Group I). The dose of extract, TME 200 (Group III) and TME 400 (Group IV) declined the elevated level of SGOT (10.19%, P<0.01, 66.3%, P<0.001), SGPT (15.41%, P<0.01, 73.2%, P<0.001), ALP (7.30%, P<0.05, 29.68%, P<0.001), BLB (12.64%, P<0.01, 53.12%, P<0.001) and promote the level of TP (17.94%, ns, 37.25%, P<0.01), ALB (21.61%, P<0.001, 26.36%, P>0.001) respectively as compared to group II. Similarly, silymarin decreased SGOT by (120.6%, P<0.001), SGPT (110.1%, P<0.001), ALP (105%, P<0.001), BLB (216%, P<0.001) and increased TP by (42.85%, P<0.001), ALB (30.57, P<0.001) as compared to group II. The results are tabulated in Table 2.

Effect of TME on body weight and liver weight

The effect of different doses of TME on body weight and liver weight were studied (Table 3). In Group II body weight decreased by 5.845% while liver weight increased by 26.36%. Animal Treated with TME at the doses of 200 and 400 mg/kg (Group III and IV) significantly increased in body weight by 2.15%, 3.81% respectively while liver weight was decreased by 1.01% and 8.56% respectively.

Effect of TME on blood parameters

The outcome in (Table 4) showed a significant change in RBC, Hb, PLT, WBC, and % Lymphocytes counts. RBC PLT, WBC, and % Lymphocytes counts significantly increased at the dose of 1000 and 2000 mg/kg, while Hb count non-significantly increases at the dose of 1000mg/kg as compared to control group. Hb, PLT, WBC and % Lymphocytes counts significantly increased at the dose of 4000 mg/kg, whereas RBC's count non-significantly increases at the dose of 4000mg/kg when compared to the control group.

Histopathological observations

The histological explanation (Figure 1) support the results obtained from serum enzyme assays. Liver sections of control rats showed normal hepatic cells with well-preserved cytoplasm and well brought out central vein. Simvastatin (20mg/kg) treated rats (Group II), displayed the massive fatty changes, necrosis, central vein congestion, ballooning degeneration, and the loss of cellular boundaries, whereas TME 200mg/kg treated groups (Group III) showed mild congestion in central vein with less fatty changes, mild necrotic cells, with minimal inflammatory conditions and less infiltration of the leucocyte's while TME 400mg/kg treated group (Group IV) showed regeneration of hepatocyte around central vein with near normal liver architecture, prominent nucleus and possessing maximum hepatoprotective action. Rats in (Group V) exhibited well

brought out central vein, hepatic cell with well-preserved cytoplasm, prominent nucleus.

DISCUSSION

The WHO survey confirmed that 70-80% of the world population rely on noncommercial medicine from herbal sources in primary health care units.[23] The results of the present study clearly indicated hepatoprotective effects of the methanolic fruits extract of *Tricoxanthes dioca* against simvastatin induced liver toxicity in rats. Liver is a vital organ within the body, playing essential role in metabolic homeostasis and detoxification of variety of drugs and xenobiotic.[24] Assessment of liver function can be performed by estimating the activities of serum SGOT, SGPT,

Table 1: Preliminary phytochemical analysis of *T. dioica* fruit extract.

S.No	Name of test	Constituents	Inference
1	Ferric Chloride & Gelatin test.	Tannin	+
2	Mayers&Wagners Test.	Alkaloids	+
3	Benedict's test.	Carbohydrates	++
4	Ferric Chloride &Shinoda Test.	Flavonoids	+
5	Keller Killiani& Bromine water test.	Glycosides	-
6	Salkowaski Test.	Steroids	+

"+" means present.

Table 2: Effect of TME on serum SGOT, SGPT, ALP, BLB, TP and ALBagainst simvastatin induced liver toxicity in rats.

Groups	SGOT	SGPT	ALP	BLB	TP	ALB
Control	31.2 ± 1.5	41.3 ± 2.1	87.32 ± 3.2	0.2 ± 0.01	6.2 ± 0.6	3.6 ± 0.01
SIM	136.2 ± 4.3†	97.35 ± 3.4†	213.1 ± 4.2†	0.98 ± 0.02†	3.2± 0.4†	2.43± 0.02†
TME200	123.6 ± 3.4^{b}	84.35 ± 3.1^{b}	198.6 ± 4.1^{a}	0.87± 0.04^{b}	3.9 ±0.3^{ns}	3.1±0.01^{c}
TME400	81.9 ± 3.1^{c}	56.2 ± 2.9^{c}	164.32 ± 3.2^{c}	0.64 ± 0.03^{c}	5.1 ± 0.2^{b}	3.3 ± 0.02^{c}
SYL 20	61.74 ± 2.9^{c}	46.32 ± 2.1^{c}	103.5 ± 3.6^{c}	0.31 ± 0.02^{c}	5.6 ± 0.4^{c}	3.5 ± 0.02^{c}

Values are mean ± S.E.M. of 6 rats in each group, ns: non-significant.
P values:†<0.001 compared with respective control group I.
P values: ^{a}<0.05, ^{b}<0.01, ^{c}<0.001 compared with group II.

Table 3: Effect of TME on body weight and liver weightagainst simvastatin induced liver toxicity in rats.

S.No	Treatment	Body weight (g)	Liver weight (g)
1	Control	172.8±1.2	6.42±0.01
2	SIM	162.7±1.3†	7.92±0.02†
3	TME200	166.2±1.3^{ns}	7.84±0.03^{b}
4	TME400	168.9±1.4^{b}	7.24±0.02^{c}
5	SYL20	170.8±1.1^{c}	6.98±0.01^{c}

Values are mean ± S.E.M. of 6 rats in each group, ns: non-significant.
P values:†<0.001 compared with respective control group I.
P values: ^{a}<0.05, ^{b}<0.01, ^{c}<0.001 compared with group II.

Table 4: Effect of TME on blood parameters against simvastatin induced liver toxicity in rats.

Parameter	Control	1000 mg/kg	2000 mg/kg	4000 mg/kg
RBC (x10^{12})	7.6 ± 0.1	8.1 ± 0.12^{a}	8.4 ± 0.13^{c}	7.9 ± 0.16^{ns}
Hb (g/dL)	13.01 ± 0.2	13.91 ± 0.3^{ns}	14.6 ± 0.4^{a}	14.4 ± 0.5^{a}
PLT (x10^{9}/L)	613.2 ± 5.6	634.6 ± 6.2^{a}	645.2 ± 4.6^{b}	653.5± 5.1^{c}
WBC (x10^{9})	8.1 ± 0.12	9.2 ± 0.2^{a}	11.5 ± 0.6^{c}	10.01 ± 0.3^{b}
Lymphocytes (%)	41.2 ± 2.1	50.3 ± 3.2^{a}	54.2 ± 3.1^{a}	58.6 ± 3.5^{b}

Values are mean ± S.E.M. of 6 rats in each group, ns: non-significant.
P values:†<0.001 compared with respective control group I.
P values: ^{a}<0.05, ^{b}<0.01, ^{c}<0.001 compared with group II.

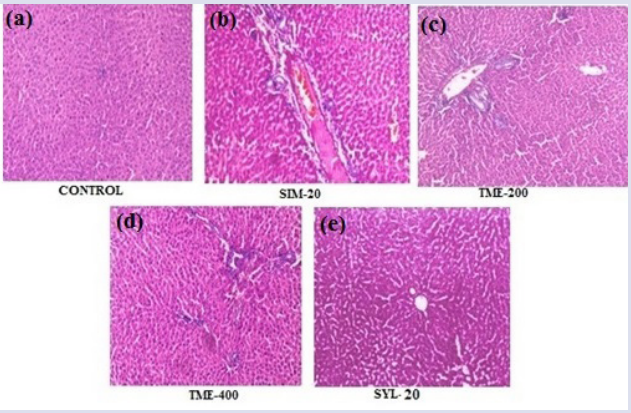

Figure 1: Histopathology of H&E stained sections of liver at 250X.
(a) Liver sections of normal control rats showed the normal hepatic cells with well-preserved cytoplasm; well brought out central vein.
(b) Liver section of SIM20 showed the massive fatty changes, necrosis, central vein congestion, ballooning degeneration, and the loss of cellular boundaries.
(c) Liver section of TME 200 showed mild congestion in central vein with less fatty changes, mild necrotic cells, with minimal inflammatory conditions, less infiltration of the leucocytes.
(d) Liver section of TME400 showed regeneration of hepatocyte around central vein with near normal liver architecture, prominent nucleus and nucleolus and possessing maximum hepatoprotective action.
(e) Liver section of rats SYL20 showed well brought out central vein, hepatic cell with well-preserved cytoplasm, prominent nucleus and nucleolus.

ALP, total bilirubin, albumin and total proteins, which are originally present in higher concentrations in hepatocytes. During liver disease, these enzymes leak into the bloodstream in conformity with the extent of liver damage.[25] Bilirubin is an index of liver function and its elevated level indicate damage to the liver and bile duct.[26] Liver damage induced by simvastatin represents disturbances of metabolism of liver cells that leads to distinctive changes in the liver serum markers. The increased levels of hepatic serum markers like SGOT, SGPT, ALP, total bilirubin and decreased in the albumin, was observed in simvastatin treated animals; this may bedue to the changes in the cell membrane permeability indicating severity of hepatocellular damage.[27,28] The animals treated with methanolic extract of *T. dioica* significantly reduced the levels of SGOT, SGPT, ALP, total bilirubin while increase total protein and albumin levels in dose dependent manner as compared with simvastatin as well as silymarin treated animals. Blood parameters dispense valuable data regarding health of animals.[29]

Administration of the plant extract resulted in significant increment inHb, PLT, WBC and % Lymphocytes counts at the dose of 4000 mg/kg. RBC and Hb are vital in transporting respiratory gases. The increment in levels of RBC and Hb implies that extract did not adversely affect oxygen carrying capacity of the blood and the amount of oxygen delivered to tissues, therefore can be used in anaemia.[30] The significant increment in the platelet count following administration of plant extract is the indication of stimulation of thrombopoietin creation as it has hemostatic capability of the blood and upholding blood clotting mechanism.[31] Inflammatory response is characterized by the involvement of WBC. In this study, the incrementin level of WBC indicates the stimulation of immune system, in retort to toxic environment.[32] Lymphocytes are the key cells of the immune system and elevation in its level indicates pathogenic attack and play the chief role in body defense mechanisms.[33,34] Increased level of WBC's and Lymphocytes suggesting that the TME extract challenge the immune system of the animals. Liver protective outcome of TME was further investigated by histopathological study. TME at different dose levels offers liver protection, but 400 mg/kg is more effective than all other inferior doses. As demonstrated in the present study, administration of simvastatin significantly elevated serum levels of hepatic enzymes, and that representing significant hepatocellular harm. Thus, our study confirmed the hepatoprotective potential of *Trichosanthes dioica* Roxb against simvastatin induced liver toxicity in rats. In fact, activity of *Trichosanthes dioica* Roxb is quite like silymarin, as reference hepatoprotective agent.

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CONFLICT OF INTEREST

No conflict of interest associated with this research work.

ABBREVIATIONS

SGOT: Serum glutamic oxaloacetic transaminase; **SGPT:** Serum glutamic pyruvic transaminase; **ALP:** Alkaline phosphatase; **SEM:** structural equation modeling; **SIM:** Simvastatin; **SLY:** Silymarin.

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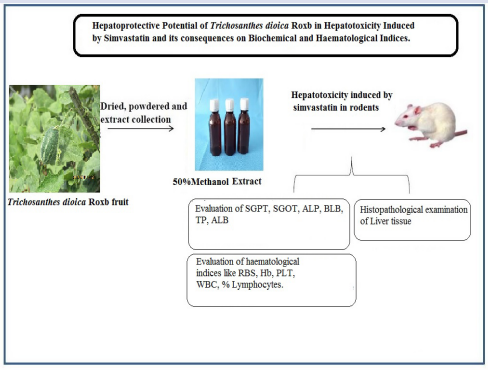
GRAPHICAL ABSTRACT



SUMMARY

- Hepatoprotective potential methanolic fruit extract of TrichosanthesdioicaRoxb was estimated along with its effect on biochemical and haematological indices in hepatotoxicity induced by simvastatin in rats. The results demonstrate the alterations in elevated levels ofSGOT, SGPT, ALP, total bilirubin and restored the total protein and albumin level. The histological study showed regeneration of hepatocytes around central vein with near normal liver architecture revealing hepatoprotective effect of fruit extract.

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