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Original Research Article

Investigation of the hepatoprotective potential of the hydroalcoholic leaves extract of *Ricinus communis* on isoniazid induced and thioacetamide induced hepatotoxicity in Wistar rats

Sushrut Oza, Reshma Shelar, Priyanka Waghulde, Swati Kolhe, Tina Saldanha*

Department of Pharmacology, AISSMS College of Pharmacy, Kennedy Road, Pune, Maharashtra, India

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***Correspondence:**
Dr. Tina Saldanha,
Email: tina_s@aissmscop.com

ABSTRACT

Background: The liver is highly susceptible to drug- and chemical-induced injury. Isoniazid and thioacetamide are known hepatotoxins that cause oxidative damage. *R. communis* leaves possess bioactive compounds with reported antioxidant and hepatoprotective potential. This study evaluated the hydroalcoholic leaf extract of *R. communis* against isoniazid and thioacetamide induced hepatotoxicity in Wistar rats.
Methods: Wistar rats were divided into five groups in each model. Each group consisted of five animals. Hepatotoxicity was induced using isoniazid (250 mg/kg, p.o., 14 days) and in another model using thioacetamide (400 mg/kg, i.p., 3 days). Test groups received *R. communis* extract at 250 and 500 mg/kg, with Liv.52 (400 mg/kg) as standard. Serum hepatic markers, body weight, liver-to-body weight ratio, and liver histology were assessed. Antioxidant activity was determined by ferric reducing antioxidant power assay. Data were analyzed using one-way ANOVA followed by Tukey's test.
Results: In the isoniazid model, RIC 250 mg/kg and 500 mg/kg significantly reduced ALT levels ($p<0.05$), however at 500 mg/kg, the extract increased AST and ALP levels. The liver-to-body weight ratio decreased significantly in treatment groups. Histology revealed minimal hepatic changes compared to moderate-to-severe injury in controls. In the thioacetamide model, *R. communis* produced mild biochemical improvement but caused mortalities in both dose groups. FRAP assay confirmed antioxidant potential (EC_{50}=12.39 µg/ml).
Conclusions: *R. communis* extract demonstrated significant hepatoprotective and antioxidant activity, particularly at 250 mg/kg. However, the inconsistent effects at a higher dose and observed mortalities in the TAA model necessitate further investigation into its safety and therapeutic window.

Keywords: Castor, FRAP assay, Hepatoprotective, Isoniazid, *Ricinus communis*, Thioacetamide

INTRODUCTION

The liver, a vital organ with diverse responsibilities, plays a key role in the metabolism of numerous drugs during phase 1 and 2 reactions. During this process, the liver converts the drugs into water-soluble compounds that can be eliminated from the body through the bile.[1]

First-generation antitubercular drugs like isoniazid (INH) and rifampicin and some herbal supplements are common causes of drug-induced liver injury and acute liver failure.[2] In 1963, the use of INH as a single treatment for preventing active tuberculosis (TB) in patients with a positive tuberculin skin test, was recommended. However, subsequent cases of severe liver damage caused by large doses of INH alone emerged.[3] Currently, INH is one of the first line treatment drugs for TB. According to the World Health Organisation, in 2021, an estimated 10.6 million people fell ill with TB worldwide.[4] This demonstrates the current extent of INH usage as a tuberculosis treatment,

which unfortunately carries the side effect of hepatotoxicity.

Another potential cause of hepatotoxicity is occupational hazards involving exposure to various chemicals and toxic substances. Thioacetamide (TAA) is an important organosulfur compound with wide industrial applications and known liver-damaging and carcinogenic properties. It is used in the leather, textile, and paper industries.[5] Scientific studies have provided substantial evidence regarding the detrimental effects of TAA on the liver. Specifically, these studies have highlighted the capacity of TAA to induce oxidative damage within the liver tissue [6]

R. communis, a member of the Euphorbiaceae family is a majorly cultivated crop in tropical and subtropical regions worldwide. It reported to contain steroids, saponins, alkaloids, flavonoids, and glycosides in phytochemical studies.[7,8] Earlier scientific investigations have demonstrated that the leaves of *R. communis* have antioxidant, antinociceptive, and anticancer activity.[9]

Of specific interest to our study were several reports on the hepatoprotective effect of different parts of the *R. communis* plant in various animal models. Specifically, the extracts of the leaves of *R. communis* have demonstrated hepatoprotective effect in paracetamol, ketoconazole, D-galactosamine, and CCl4 induced hepatic damage models.[1,10,11] This combined with its reported antioxidant activity makes it a suitable candidate for investigation of its hepatoprotective effect against INH and TAA induced liver toxicity.[12] To the best of our knowledge, there are no scientific reports regarding the hepatoprotective effect of the hydroalcoholic leaves extract of *R. communis* in INH and TAA induced hepatotoxicity in rats. Therefore, this study was the first to investigate the hepatoprotective effects of the hydroalcoholic leaf extract of *R. communis* against INH- and TAA-induced hepatotoxicity, with a specific focus on its in-vitro antioxidant capacity as a potential mechanism.

METHODS

INH was purchased from LOBA Chemie Pvt. Ltd. TAA was purchased from Chemscope Lab Solutions India LLP, Mumbai. Liv.52 (Himalaya Wellness Company), a standard marketed formulation popularly used for its hepatoprotective effect was purchased from a local pharmacy shop. The hydroalcoholic extract of *R. communis* leaves was purchased from Shamantak Enterprises, Pune. The hepatic marker enzymes ALT and AST were estimated using commercial kits from Meril Diagnostics Private Limited, India. Estimation of ALP and Bilirubin was done by commercial kits from Pathozyme Diagnostics.

Wistar rats of either sex weighing 200-320 gm were used for the study. They were maintained under standard laboratory conditions, including controlled temperature, humidity, and a 12-hour light-dark cycle. The animals were provided with a standard pellet diet and water ad libitum throughout the experimental period.

All experimental procedures were carried out in strict compliance with the ethics and guidelines for animal care and use in research. The protocol was approved by the Institution Review Committee CPCSEA/IAEC/PT-02/02-2K22 on 27/12/2022. The studies were conducted in the animal house of AISSMS College of Pharmacy, Pune, during the period from January 2023 to March 2023.

Experimental design (INH model)

A total of twenty-five Wistar rats were randomly divided into five groups, with five animals in each group. The groups were as follows: Group 1 served as the normal control and received Sodium CMC (p.o.) for 14 days. Group 2 served as the INH control and received sodium CMC (p.o.) and INH 250 mg/kg/day (p.o.) for 14 days. Group 3 and 4 (test groups) received RIC 250 mg/kg/day (p.o.) and RIC 500 mg/kg/day (p.o.) respectively along with concurrent administration of INH 250 mg/kg/day (p.o.) for 14 days. Group 5 standard treatment group received Liv.52 400 mg/kg/day (p.o.) along with INH 250 mg/kg/day (p.o.) for 14 days.

Experimental design (TAA model)

A total of twenty-five Wistar rats were randomly divided into five groups, with five animals in each group. The groups were as follows, group 1 served as the normal control group and received sodium CMC from day 1 to day 6 (p.o.) alongside saline from day 4 to day 6 intraperitoneally (i.p.), Group 2 served as a TAA control group was administered sodium CMC from day 1 to day 6 (p.o.), followed by TAA at a dosage of 400 mg/kg i.p. on last 3 days of the study, group 3 and group 4 served as test groups, underwent administration of RIC at a dosage of 250 mg/kg and 500 mg/kg per day (p.o.) from day 1 to day 6 and followed by TAA at a dose of 400 mg/kg i.p. on the last 3 days of the study, Group 5 served as a standard group, was administered Liv.52 at a dosage of 400 mg/kg per day (p.o.) from day 1 to day 6, along with TAA at 400 mg/kg i.p. on the last 3 days of the study.

In the INH model on the fifteenth day and in the TAA model on the 7th day, the blood was collected by retro-orbital puncture under light anesthesia, and serum was separated by centrifugation. The serum liver injury markers AST, ALT, ALP and bilirubin were estimated using commercially available kits. The rats were sacrificed by cervical dislocation. The livers of all the animals were rinsed using physiological saline. Liver weight and morphology were noted. Slices of the liver were fixed in 10% formalin for histological studies.

Based on previous studies involving the INH induced hepatotoxicity model in rats, the histopathological study evaluated vascular changes such as congestion and hemorrhages in the hepatic parenchyma. Degenerative

changes of hepatocytes were examined, specifically focusing on granular cytoplasm and vacuolar changes, as well as cellular swelling and karyomegaly of the hepatic nucleus. Also, necrotic changes of hepatocytes, characterized by the loss of the nucleus, infiltration of mononuclear inflammatory cells in the hepatic parenchyma and peri-portal MNC infiltration. Presence of fatty infiltration in the cytoplasm of hepatocytes was also a part of histopathological examination.[13]

Similarly for the TAA induced hepatotoxicity model, various parameters like necrosis of liver cells, inflammation of hepatocytes, hepatocellular vacuolation, polymorphonuclear leucocyte infiltration, mononuclear inflammatory cellular infiltration were evaluated.[14]

The *in vitro* ferric reducing antioxidant power (FRAP) assay was conducted for determination of antioxidant potential of Ricinus extract according to the procedure given by Benzie and Strain.[15] Briefly, the FRAP reagent consisted of 25 ml of Acetate buffer, 2.5 ml of 2,4,6-tripyridyl-s-triazine (TPTZ) in HCl solution, and 2.5 ml of ferric chloride solution. The test samples were mixed with the FRAP reagent in various concentrations, and the volume was adjusted using distilled water. The absorbance of both the test samples and different concentrations of ascorbic acid, used as a standard, was measured at 593 nm to calculate the EC50 (effective concentration) value. Statistical analysis was performed using GraphPad Prism 8.4.3 software. One-way Analysis of Variance (ANOVA) followed by Tukey's multiple comparisons test was performed to determine the statistical significance. The data were expressed as mean ± standard error of mean (SEM). A p value of less than 0.05 was considered statistically significant.

RESULTS

Effect of the hydroalcoholic leaves extract of R. communis on serum hepatic markers in INH induced hepatotoxicity in rats

Administration of INH for 14 days resulted in significant alterations in serum hepatic markers, as summarized in Table 1. However, these increases were statistically significant only for ALT and bilirubin levels as compared to the control group. Treatment with RIC 250 as well as Liv.52 significantly decreased ALT levels compared to the INH control group. With respect to the other liver markers, the treatments did not show any significant difference compared to the INH control group and AST levels were, in fact, marginally higher ($p>0.05$). The INH control group had a very significant increase in bilirubin levels compared to the control group. Although the treatments demonstrated a decreasing trend in the serum bilirubin levels it was not found to be significantly different from the INH control ($p>0.05$).

Table 1: Effect of the hydroalcoholic leaves extract of *R. communis* on serum hepatic markers in INH induced hepatotoxicity in rats.

	AST (U/L)	ALT (U/L)	ALP (U/L)	Bilirubin (mg/dl)
Control	119.37±25.50	41.3±4.18	110.8±7.37	0.86±0.11
INH Control	198.02±37.06	103.48±14.64$^{\#\#}$	143.62±13.74	1.46±0.13$^{\#\#}$
RIC 250	187.1±9.63	54.95±7.20*	138.025±8.45	1.14±0.07
RIC 500	242.9±25.98	87.17±11.74	153.75±6.40	1.39±0.06
Liv.52	203.82±12.66	56.85±8.52*	137.3±4.28	1.075±0.08

(ALT: Alanine aminotransferase, AST: Aspartate aminotransferase, ALP: Alkaline phosphatase, INH: Isoniazid, RIC 250: *R. communis* 250 mg/kg dose, RIC 500 : *R. communis* 500 mg/kg dose) Values are expressed as mean ± SEM (n=5). $^{\#\#}$ $p<0.01$ versus Normal Control; * $p<0.05$ versus INH Control

Effect of the hydroalcoholic leaves extract of R. communis on body weights and liver/body weight ratio of INH induced hepatotoxicity in rats

Histopathological examination of liver tissues from the INH model revealed minimal to mild pathological changes in treatment groups, as depicted in Figure 1. The control group exhibited no abnormalities across all observed parameters.

In the INH control group, mild vascular changes such as congestion and hemorrhages were observed, along with moderate degenerative changes in hepatocytes, characterized by granular cytoplasm and vacuolar alterations. Hepatocytes also exhibited moderate fatty infiltration in their cytoplasm, accompanied by minimal infiltration of mononuclear inflammatory cells. In the RIC250 and RIC500 treatment groups, livers displayed minimal to mild pathological changes across all measured parameters, regardless of the administered dose. The Liv.52 group, on the other hand, exhibited only minimal vascular changes and minimal fatty infiltration in the cytoplasm of hepatocytes.

The effects of *R. communis* extract on body weight and liver-to-body weight ratio in INH-induced hepatotoxicity are presented in Table 2. All the groups exposed to INH, except Liv.52, demonstrated varying degrees of weight loss which was significantly different from the control group. Although RIC and Liv.52 treated groups were

associated with lesser weight loss than the INH control, this was not found to be statistically significant (p>0.05).

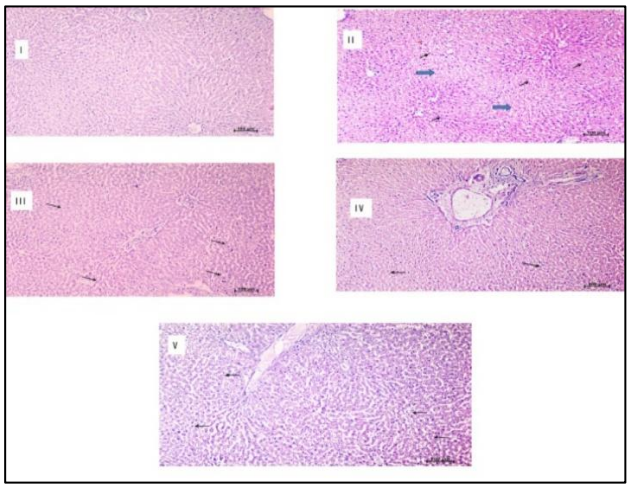

Figure 1: Effect of the hydroalcoholic leaves extract of *R. communis* on liver histopathological changes in INH-induced hepatotoxicity in rats: (I) Normal control showing typical hepatic architecture; (II) INH control exhibiting moderate fatty infiltration (black arrows) and vacuolar degeneration (blue arrow); (III and IV) RIC 250 and 500 mg/kg treated groups showing minimal to mild pathological changes; (V) Liv.52 treated group demonstrating significant protection with near-normal histology.

The L/BW ratio of the INH control group was found to be significantly higher than that of the control group. There was a significant decrease in L/BW of RIC 250 (p<0.01), RIC 500 (p<0.001) and Liv.52 (p<0.0001) groups.

Effect of the hydroalcoholic leaves extract of R. communis on serum hepatic markers in TAA induced hepatotoxicity in rats

Serum hepatic marker levels following TAA-induced hepatotoxicity and treatment with *R. communis* extract are shown in Table 3. Administration of TAA in high doses significantly resulted in elevation in the serum levels of liver enzyme markers AST and ALP (p<0.05) and total bilirubin (p<0.01) as compared to the control group.

Liv.52 showed a significant decrease in AST levels as compared to the TAA control group p<0.05). RIC 250 was able to reduce the levels of ALT, AST, ALP and bilirubin levels but the decrease was not significant (p>0.05). The same was with the case with the RIC 500 group except for the bilirubin parameter unexpectedly which was not changed. 2 mortalities were observed in each RIC 250 and RIC 500 groups.

Liver sections from TAA-induced hepatotoxicity models showed moderate inflammation and necrosis, with treatment groups exhibiting milder responses, as illustrated in Figure 2.

Table 2: Effect of the hydroalcoholic leaves extract of *R. communis* on % decrease in body weight and Liver/body weight ratio in INH induced hepatotoxicity in rats.

	% decrease in body weight	Liver/body weight (gm/gm)
Control	0.256±1.43%	0.028±0.00041
INH control	19.44±1.35%####	0.034±0.00082###
RIC 250	11.660±0.98%**	0.030±0.00070**
RIC 500	16.230±0.75%	0.029±0.00062***
Liv.52	7.078±2.11%****	0.027±0.00085****

Values are expressed as mean±SEM (n=5). #### p<0.0001 vs. normal control for body weight; ### p<0.001 vs. normal control for liver/body weight; ** p<0.01, *** p<0.001, **** p<0.0001 vs. INH control.

Table 3: Effect of the hydroalcoholic leaves extract of *R. communis* on serum hepatic markers in TAA induced hepatotoxicity in rats.

Group	ALT (U/l)	AST (U/l)	ALP (U/l)	Bilirubin (mg/dl)
Control	143.6±20.63	209.25±8.32	126.12±13.60	0.75±0.058
TAA Control	209.56±19.29	353±48.67#	195.22±16.70#	1.234±0.088##
RIC 250	157.73±14.39	254.8±35.61	161.4±6.90	1.133±0.080
RIC 500	175.93±38.13	344.36±53.55	162.77±17.08	1.26±0.085
Liv.52	143.52±14.38	178.96±21.08*	151.02±13.18	1.044±0.085

TAA: Thioacetamide, ALT: Alanine aminotransferase, AST: Aspartate aminotransferase. Values are expressed as mean ± SEM (n=5/group; note mortalities in RIC groups). # p<0.05, ## p<0.01 vs. Normal Control; * p<0.05 vs. TAA Control.

All the groups that received TAA showed increased necrosis. The TAA control and Liv.52 groups exhibited moderate inflammation, while RIC 250 and RIC 500 showed milder responses. Neither RIC nor Liv.52 was able to reduce hepatocellular vacuolation. Polymorphonuclear leukocyte infiltration was moderate in TAA control and Liv.52. RIC treatments were able to suppress

polymorphonuclear leukocyte infiltration. Lastly, mononuclear inflammatory cellular infiltration was moderate in the TAA control group, whereas RIC 250, RIC 500 and Liv.52 exhibited milder responses.

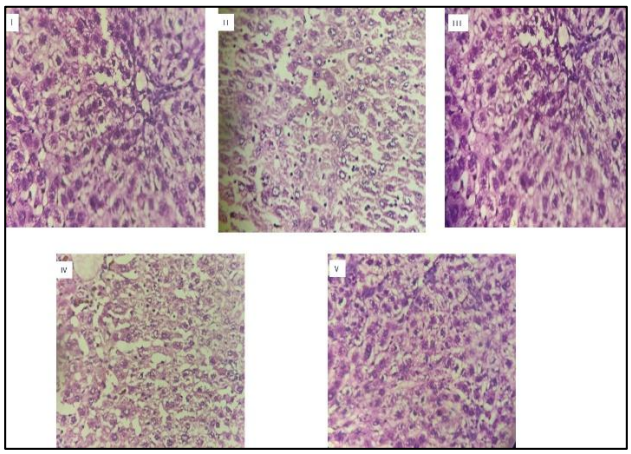

Figure 2: Effect of the hydroalcoholic leaves *extract R. communis* on liver histopathological changes in TAA induced hepatotoxicity in rats: (I) Normal control with intact liver structure; (II) TAA control showing severe necrosis (N), inflammation (green arrow), and vacuolation (V); (III and IV) RIC 250 and 500 mg/kg treated groups showing reduced necrosis and inflammation; (V) Liv.52 treated group exhibiting marked hepatoprotection.

The FRAP assay demonstrated the antioxidant capacity of *R. communis* hydroalcoholic leaves extract through an EC50 (effective concentration) of 12.39 µg/ml, while ascorbic acid exhibited an EC50 of 0.637 µg/ml.

DISCUSSION

The present study aimed to evaluate the hepatoprotective potential of the hydroalcoholic leaves extract of *R. communis* against INH-induced and TAA induced hepatotoxicity in Wistar rats. INH, despite its antitubercular properties, is known to have a serious side effect of hepatotoxicity. This hepatotoxicity is attributed to the induction of cytochrome P-450, which leads to the formation of toxic metabolites and subsequent hepatocellular damage. Additionally, oxidative stress resulting from the suppression of the antioxidant system has also been implicated in hepatocellular damage caused by INH. In this study, hepatotoxicity was noted following the administration of INH for a duration of 14 days at a dosage of 250 mg/kg, this corroborates the findings of the previously published research.[16] A significant reduction in body weight was observed in the INH control group compared to the normal control, consistent with previous findings.[17] Our study protocol followed concurrent treatment of INH and hydroalcoholic leaves extract of *R. communis.* Treatment with the extract at a dose of 250 mg/kg and the standard treatment of Liv.52 at 400 mg/kg resulted in a significant reduction in the ALT levels. ALT is recognized as a highly sensitive and reliable indicator of liver damage.[18] Therefore, since our extract has demonstrated a significant reduction in ALT levels, it suggests that the extract administered at a dose of 250 mg/kg and Liv.52 at 400 mg/kg has the potential to offer hepatoprotective effects. The extract also showed a marginal though not statistically significant decrease in AST, ALP, and serum bilirubin levels ($p>0.05$). However, when the dose was increased to 500 mg/kg, it was observed that only ALT and serum bilirubin levels were reduced as compared to INH control ($p>0.05$). Paradoxically at 500 mg/kg the AST levels and ALP levels slightly increased than the INH control group. This may indicate a dose-dependent response, with a higher dose potentially leading to a differential effect on the liver enzymes. An elevated L/BW ratio is a classic sign of hepatomegaly which is commonly caused by the accumulation of fat, inflammatory cell infiltration, and cellular swelling. Consequently, a significant decrease in this ratio in treatment groups demonstrates the efficacy of an intervention in reducing liver enlargement and mitigating underlying histopathological damage.[19] The fact that the treatment groups had significantly lower L/BW ratios suggests that they were able to protect the liver from damage. TAA is used for its application in triggering liver injury in rats.[20] Scientific studies have provided substantial evidence regarding the detrimental effects of TAA on the liver. Specifically, these studies have highlighted the capacity of TAA to induce oxidative damage within the liver tissue.[6]

In the TAA control group, a significant increase in the levels of AST, ALP and bilirubin was observed and a non-significant increase was noted in ALT levels as compared to the control group. This increase in enzyme levels is indicative of hepatocellular damage and impaired liver function. confirming the successful induction of hepatotoxicity by 3 i.p. doses of TAA at 400 mg/kg dose level similar to the research conducted by Bruck et.al.[21] Interestingly, treatment with *R. communis* extracts at both doses, 250 mg/kg and 500 mg/kg, resulted in observable variations in the liver injury biomarker levels. The RIC 250 group lowered the levels of ALT, AST, ALP, and Bilirubin compared to the TAA control group, but these decreases were not statistically significant ($p>0.05$). Paradoxically the RIC 500 group, which received a higher dose of Ricinus extract, did not exhibit a consistent improvement in liver enzyme levels compared to the TAA control group which suggests that the higher dose of 500 mg/kg did not provide the same hepatoprotective benefits. Liv.52, the positive control, demonstrated a significant reduction in AST levels and notable but non-significant decrease in ALT, ALP and bilirubin levels as compared to the TAA control group, indicating its efficacy in ameliorating hepatocellular damage.

The observed capacity of *R. communis* leaves extract to decrease the serum hepatic marker enzymes could be attributed to its antioxidant properties.[1] The leaves of *R. communis* are known to possess antioxidant compounds

that may counteract the oxidative damage caused by INH treatment, thus protecting the hepatocytes from damage. RIC 250 and RIC 500 groups reduced inflammation in histopathological study as compared to the TAA control group signifying that our extract possessed anti-inflammatory properties.[22] Two mortalities were observed in each RIC 250 and RIC 500 groups of the TAA treated rats. The occurrence of mortalities in these groups raises important safety considerations that warrant further investigation before considering its therapeutic use. Earlier pharmacological studies with hydroalcoholic leaves extract have not reported any mortalities up to 500 mg/kg dose for 14 days. The acute toxicity studies of the extract are reported to be upto 8000 mg/kg.[23] The occurrence of mortalities in the TAA model, but not in the INH model, points to a possible adverse interaction between TAA and the extract.

The FRAP assay revealed that the hydroalcoholic leaves extract of RIC possesses antioxidant capacity, although at a lower level compared to ascorbic acid. This confirmed antioxidant activity provides a plausible mechanism for the observed reduction in oxidative stress-mediated liver injury. *R. communis* leaves extract's effectiveness in neutralizing free radicals might be due to the phytochemicals present within the extract such as ricinine and N-demethyl ricinine.[1,24] The study was limited by a relatively small sample size and short study duration, which may not fully capture the long-term hepatoprotective or toxic effects of *R. communis* extract. Moreover, inconsistent biochemical responses at higher doses and observed mortalities in the TAA model indicate potential dose-dependent toxicity.

CONCLUSION

In conclusion, at a dose of 250 mg/kg, the extract showed hepatoprotective effects by decreasing serum liver biomarkers in both the models. However, caution is needed due to mixed effects observed at the higher dose of 500 mg/kg. In the TAA model, mortality in the treatment groups raised safety concerns. The standard treatment of Liv.52 was able to show the hepatoprotective action in both the models. The histopathological examination supported the findings showing minimal to mild pathological changes in test treated groups in both studies. The FRAP assay demonstrated the extract's antioxidant capacity.

Further investigations are needed to identify dose and the active constituents responsible for the hepatoprotective effects and validate the extract's potential as a natural hepatoprotective agent.

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