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In-Vivo Evaluation of the Hepatoprotective Potential of Hedyotis aspera against Isoniazid and Rifampicin-Induced Liver Injury in Wistar Rats

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Abstract

Drug-induced liver toxicity is a significant contributor to hepatic damage and is frequently linked with the use of antitubercular medications such as Isoniazid and Rifampicin. The present investigation was designed to assess the hepatoprotective effect of the methanolic extract of *Hedyotis aspera* against liver injury produced by these drugs in experimental rats.

Liver toxicity was experimentally induced in Wistar albino rats through oral administration of isoniazid (200 mg/kg) and rifampicin (200 mg/kg). The animals were allocated into five experimental groups comprising a normal control group, a disease control group, a standard treatment group, and two test groups treated with the methanolic extract of *Hedyotis aspera* (MEHA) at doses of 200 mg/kg and 400 mg/kg. Several biochemical indicators of liver function, including serum glutamic oxaloacetic transaminase (SGOT), serum glutamic pyruvic transaminase (SGPT), alkaline phosphatase (ALP), total bilirubin, and total protein, were measured. In addition, liver tissues were subjected to histopathological examination to evaluate structural alterations.

Rats treated with isoniazid and rifampicin exhibited a marked increase in liver enzyme levels, confirming the occurrence of hepatic damage. Administration of MEHA significantly lowered these elevated biochemical markers and improved the structural integrity of liver tissue when compared with the disease control group. The protective effect observed with the extract was comparable to that of the reference hepatoprotective drug Silymarin.

Overall, the results indicate that *Hedyotis aspera* possesses considerable hepatoprotective properties. This activity may be attributed to the presence of bioactive phytochemicals, particularly flavonoids and phenolic compounds, which are known for their antioxidant potential.

Keywords: Hepatoprotective activity, *Hedyotis aspera*, Isoniazid, Rifampicin, Liver injury, Medicinal plants.

1. Introduction

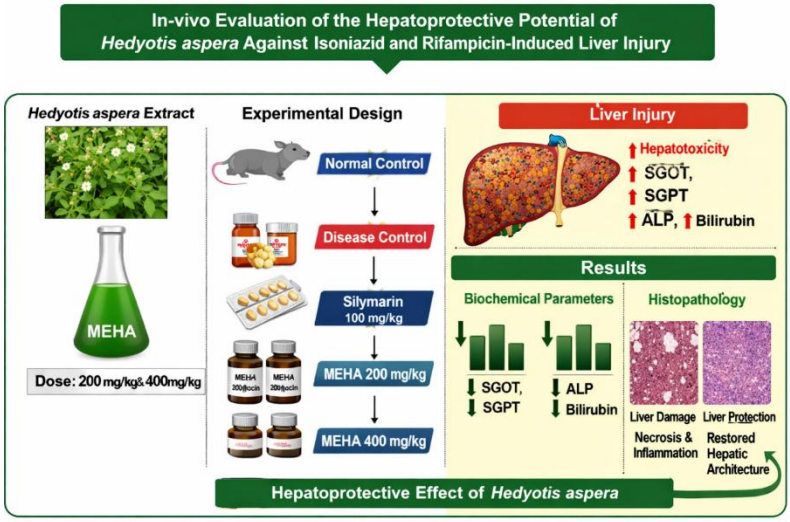
The liver is a vital organ responsible for maintaining physiological homeostasis, performing critical functions such as metabolism, detoxification of xenobiotics, and synthesis of essential biomolecules. Drug-induced liver injury (DILI) represents a significant clinical challenge and

is a leading cause of acute liver failure worldwide. Such hepatotoxicity is often mediated by oxidative stress and cellular damage resulting from reactive metabolites of therapeutic agents (Zhuang et al., 2022). Among commonly prescribed medications, antitubercular drugs like isoniazid (INH) and rifampicin (RIF) are highly effective against tuberculosis but are also well-documented for their potential hepatotoxic effects. Co-administration of INH and RIF has been shown to exacerbate the production of reactive oxygen species (ROS) and toxic intermediates, leading to lipid peroxidation, depletion of glutathione reserves, mitochondrial dysfunction, and eventual liver injury (Zhuang et al., 2022; Sankar et al., 2015). Clinically and experimentally, such toxicity is reflected by elevated serum liver enzymes, structural histopathological changes, and compromised hepatic function.

Recently, attention has turned toward medicinal plants as a safer and potentially effective approach for managing liver disorders. Bioactive phytochemicals, including flavonoids, phenolic compounds, alkaloids, and terpenoids, have demonstrated hepatoprotective capabilities through mechanisms such as antioxidative action, anti-inflammatory effects, stabilization of hepatocyte membranes, and enhancement of endogenous antioxidant defenses (Gonfa et al., 2024). Comprehensive reviews indicate that plant-derived compounds can mitigate chemically induced liver injury, positioning them as promising therapeutic candidates for DILI management.

Hedyotis aspera, a member of the Rubiaceae family commonly found in tropical regions, has been used traditionally for its medicinal properties. Phytochemical analyses reveal the presence of various bioactive compounds with antioxidant activity; however, scientific evidence supporting its protective effects against antitubercular drug-induced liver injury remains scarce (Prasanth et al., 2023). Studies on related species, such as *Hedyotis corymbosa*, have demonstrated hepatoprotective effects in experimental models, providing further rationale for investigating the genus for liver protection (Lina et al., 2018).

In light of these observations, the present study was undertaken to assess the hepatoprotective potential of the methanolic extract of *Hedyotis aspera* in a rat model of INH- and RIF-induced hepatotoxicity, focusing on biochemical markers, histopathological changes, and oxidative stress parameters.



2. Materials and Methods

Hedyotis aspera (Heyne ex Roth) was collected from P.S.C. & K.V.S.C. Government College, Nandyal, India. The plant material was authenticated by Prof. Smt. V. J. Sailajarani, a plant taxonomist from the Department of Botany. A voucher specimen was deposited in the institutional herbarium for future reference.

2.1 Plant Material Collection

The whole plant of *Hedyotis aspera* was collected from local areas and authenticated by a qualified botanist. The plant material was shade-dried and powdered for extraction.

2.2 Preparation of Extract

The dried plant material was powdered and subjected to extraction with methanol using a Soxhlet extraction apparatus. The obtained extract was then concentrated with the help of a rotary evaporator, and the concentrated extract was preserved at 4 °C until further use.

2.3 Experimental Animals

Female Wistar rats weighing between 150–200 g were procured from Raghavendra Enterprises, Bangalore. The animals were maintained under standard laboratory conditions, including a temperature of 25 ± 5°C, a 12-hour light/dark cycle, and were provided with standard pellet diet (Pravan Agro Ltd., India) and water ad libitum.

The experimental protocol was approved by the Institutional Animal Ethics Committee of Santhiram College of Pharmacy (Approval No: 1519/PO/Re/S/11/CPCSEA/2025/002).

2.4 Experimental Design

Animals were divided into five groups (n = 6).

Group	Treatment	Purpose
I	Vehicle	To serve as a normal animal
II	Isoniazid & rifampicin (200mg/kg, p.o)	To serve as a control
III	isoniazid (200 mg/kg, p.o), rifampicin (200 mg/kg, p.o) and Silymarin (100 mg/kg, p.o)	To serve as a standard
IV	isoniazid (200 mg/kg, p.o), rifampicin (200 mg/kg, p.o) and MEHA (200 mg/kg, p.o)	Low Dose
V	isoniazid (200 mg/kg, p.o), rifampicin (200 mg/kg, p.o) and MEHA (400 mg/kg, p.o)	High Dose

2.5 Biochemical Analysis

At the conclusion of the experimental study, blood samples were collected from rats that had been fasted overnight. The collection was performed through retro-orbital puncture while the animals were kept under mild anesthesia to minimize discomfort. The collected blood was left undisturbed at room temperature to allow clot formation and was then centrifuged at 3000 rpm for about 10 minutes in order to separate a clear layer of serum. The obtained serum was subsequently used for the assessment of different biochemical markers. These included serum glutamic oxaloacetic transaminase (SGOT), serum glutamic pyruvic transaminase (SGPT), alkaline phosphatase (ALP), total bilirubin, and total protein. The estimation of these

parameters was carried out using standard diagnostic kits, following the procedures and instructions provided by the manufacturer.

2.5.1 Estimation of Serum SGOT (AST)

The level of serum SGOT was determined by an enzymatic colorimetric technique based on the method developed by Reitman and Frankel. In this assay, the SGOT enzyme facilitates the transfer of an amino group from L-aspartate to α-ketoglutarate, resulting in the formation of oxaloacetate and glutamate. The oxaloacetate produced during the reaction subsequently interacts with 2,4-dinitrophenylhydrazine (DNPH), leading to the formation of a colored hydrazone compound. The intensity of this color was measured using a spectrophotometer at a wavelength of 505 nm. The activity of the enzyme was then calculated and expressed as units per liter (U/L).

2.5.2 Estimation of Serum SGPT (ALT)

Serum SGPT levels were measured using the colourimetric method described by Reitman and Frankel. In this method, the SGPT enzyme catalyses the transfer of an amino group from L-alanine to α-ketoglutarate, resulting in the formation of pyruvate and glutamate. The pyruvate produced in the reaction subsequently reacts with 2,4-dinitrophenylhydrazine (DNPH) to form a colored complex. The intensity of this colour was determined spectrophotometrically at a wavelength of 505 nm. The enzymatic activity of SGPT was then calculated and reported in units per litre (U/L).

2.5.3 Estimation of Serum Alkaline Phosphatase (ALP)

Serum ALP activity was determined using a colorimetric method that relies on the hydrolysis of p-nitrophenyl phosphate (pNPP). In this assay, the enzyme alkaline phosphatase catalyzes the breakdown of pNPP under alkaline conditions, producing p-nitrophenol and phosphate. The p-nitrophenol formed during the reaction develops a yellow color. The intensity of this yellow colored product was measured using a spectrophotometer at a wavelength of 405 nm. The resulting enzyme activity was then calculated and expressed in units per liter (U/L).

2.5.4 Estimation of Total Bilirubin

Serum total bilirubin was determined using the diazo reaction method. In this procedure, bilirubin present in the serum reacts with diazotized sulfanilic acid, resulting in the formation of a colored compound known as azobilirubin. The intensity of the developed color was then measured using a spectrophotometer at a wavelength of 540 nm. Based on this measurement, the concentration of bilirubin in the sample was calculated and expressed in milligrams per deciliter (mg/dL).

Serum total protein levels were measured using the Biuret method. In this assay, the proteins present in the serum interact with copper ions in an alkaline environment, leading to the formation of a violet-colored complex. The intensity of the violet color produced is directly proportional to the amount of protein present in the sample. This color intensity was measured spectrophotometrically at a wavelength of 546 nm. The total protein concentration was then calculated and expressed in grams per deciliter (g/dL).

2.6 Histopathological Examination

Liver tissues were collected and fixed in 10% formalin. The tissues were processed, sectioned, and stained with haematoxylin and eosin for microscopic examination.

2.7 Statistical Analysis

Results were expressed as mean ± SEM. Data were analyzed using one-way ANOVA followed by Dunnett's test. Values of **$p < 0.05$** were considered statistically significant.

3. Results

3.1 Effect on Serum Biochemical Parameters

Administration of isoniazid and rifampicin resulted in a marked elevation in the levels of SGOT, SGPT, ALP, and bilirubin in the disease control group when compared with the normal control group. However, treatment with the methanolic extract of *Hedyotis aspera* (MEHA) at doses of 200 mg/kg and 400 mg/kg significantly lowered these elevated enzyme levels. Among the two doses tested, the higher dose (400 mg/kg) exhibited a more pronounced hepatoprotective effect and its activity was found to be comparable with that of the standard drug silymarin.

3.2 Effect of MEHA on Serum SGOT (AST) Levels

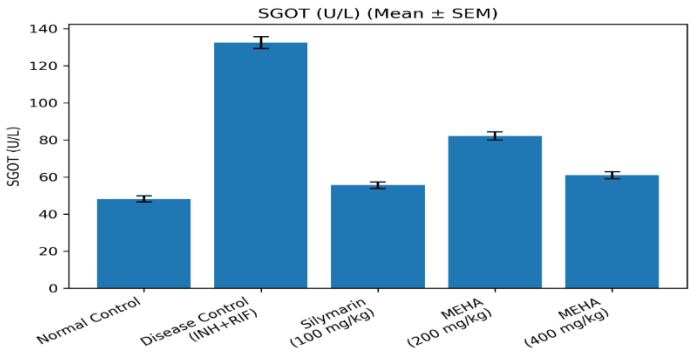
Administration of isoniazid and rifampicin caused a marked increase in serum SGOT levels in the disease control group compared with the normal control group, which indicates considerable damage to the liver cells.

Treatment with the methanolic extract of *Hedyotis aspera* (MEHA) led to a significant decrease in the elevated SGOT levels. This reduction was found to be dose-dependent, where the higher dose of 400 mg/kg produced a stronger hepatoprotective effect than the lower dose of 200 mg/kg. Moreover, the SGOT levels observed in the group treated with the higher dose of MEHA were almost similar to those seen in the group treated with the standard drug, silymarin.

Table 1. Effect of MEHA on Serum SGOT Levels

Group	Treatment	SGOT (U/L) Mean ± SEM
Group I	Isoniazid & rifampicin (200mg/kg, p.o)	48.21 ± 1.62
Group II	isoniazid (200 mg/kg, p.o), rifampicin (200 mg/kg, p.o) and Silymarin (100 mg/kg, p.o)	132.45 ± 3.12***
Group III	isoniazid (200 mg/kg, p.o), rifampicin (200 mg/kg, p.o) and MEHA (200 mg/kg, p.o)	55.63 ± 1.78###
Group IV	isoniazid (200 mg/kg, p.o), rifampicin (200 mg/kg, p.o) and MEHA (400 mg/kg, p.o)	82.17 ± 2.21**
Group V	Isoniazid & rifampicin (200mg/kg, p.o)	60.94 ± 1.85###

Values expressed as Mean ± SEM (n = 6), ***p < 0.001 vs normal control, **p < 0.01 vs disease control, ###p < 0.001 vs disease control



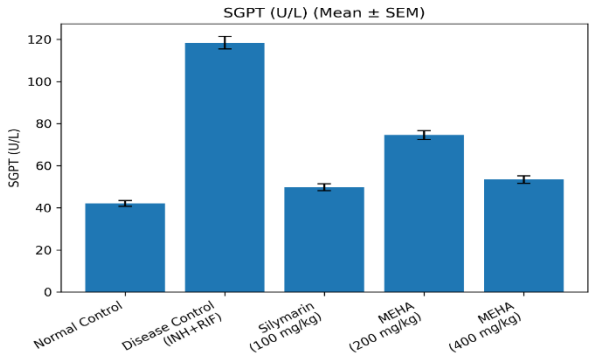
3.3 Effect of MEHA on Serum SGPT (ALT) Levels

Rats treated with isoniazid and rifampicin showed a significant increase in serum SGPT levels when compared with the normal control group, indicating damage to the liver cells. However, treatment with MEHA at doses of 200 mg/kg and 400 mg/kg markedly reduced the SGPT levels in comparison with the disease control group. The higher dose of MEHA (400 mg/kg) produced a more pronounced reduction in SGPT levels and exhibited hepatoprotective activity that was comparable to the standard drug, silymarin.

Table 2. Effect of MEHA on Serum SGPT Levels

Group	Treatment	SGPT (U/L) Mean ± SEM
Group I	Isoniazid & rifampicin (200mg/kg, p.o)	42.15 ± 1.41
Group II	isoniazid (200 mg/kg, p.o), rifampicin (200 mg/kg, p.o) and Silymarin (100 mg/kg, p.o)	118.37 ± 2.96***
Group III	isoniazid (200 mg/kg, p.o), rifampicin (200 mg/kg, p.o) and MEHA (200 mg/kg, p.o)	49.84 ± 1.67###
Group IV	isoniazid (200 mg/kg, p.o), rifampicin (200 mg/kg, p.o) and MEHA (400 mg/kg, p.o)	74.56 ± 2.03**
Group V	Isoniazid & rifampicin (200mg/kg, p.o)	53.42 ± 1.79###

Values expressed as Mean ± SEM (n = 6), ***p < 0.001 vs normal control, **p < 0.01 vs disease control, ###p < 0.001 vs disease control



3.4 Effect of MEHA on Serum ALP Levels

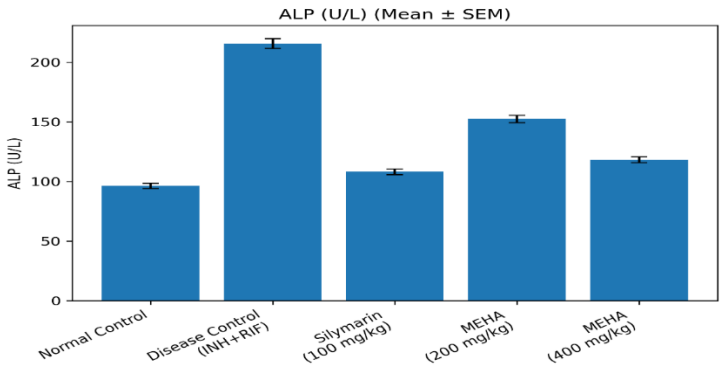
Administration of isoniazid and rifampicin led to a significant rise in serum ALP levels in the disease control group when compared with the normal control group. This increase indicates the presence of cholestasis and impairment of hepatobiliary function. Treatment with MEHA

markedly decreased the elevated ALP levels, and the reduction was found to be dose-dependent. The group treated with the higher dose (400 mg/kg) showed a substantial decline in ALP levels and demonstrated hepatoprotective activity similar to that observed with the standard drug, silymarin.

Table 3. Effect of MEHA on Serum ALP Levels

Group	Treatment	ALP (U/L) Mean ± SEM
Group I	Isoniazid & rifampicin (200mg/kg, p.o)	96.34 ± 2.14
Group II	isoniazid (200 mg/kg, p.o), rifampicin (200 mg/kg, p.o) and Silymarin (100 mg/kg, p.o)	215.72 ± 4.08***
Group III	isoniazid (200 mg/kg, p.o), rifampicin (200 mg/kg, p.o) and MEHA (200 mg/kg, p.o)	108.16 ± 2.36###
Group IV	isoniazid (200 mg/kg, p.o), rifampicin (200 mg/kg, p.o) and MEHA (400 mg/kg, p.o)	152.45 ± 3.11**
Group V	Isoniazid & rifampicin (200mg/kg, p.o)	118.28 ± 2.54###

Values expressed as Mean ± SEM (n = 6) , ***p < 0.001 vs normal control, **p < 0.01 vs disease control, ###p < 0.001 vs disease control



3.5 Effect of MEHA on Serum Total Bilirubin Levels

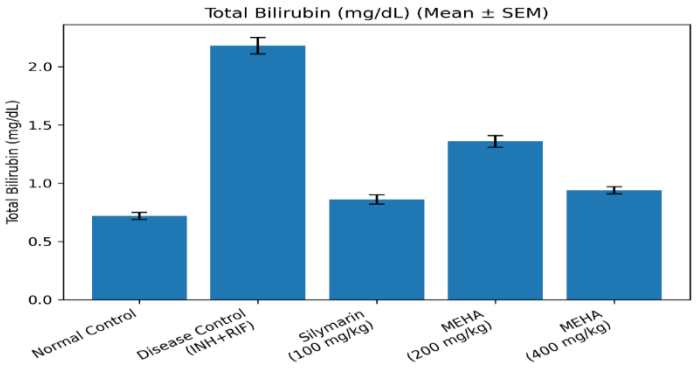
Following the administration of isoniazid and rifampicin, the disease control group showed a significant rise in total bilirubin levels when compared with the normal control group, indicating impairment of liver function. However, treatment with MEHA significantly lowered the serum bilirubin levels in both treatment groups. The higher dose (400 mg/kg) produced a more noticeable reduction and exhibited hepatoprotective activity similar to that of the standard drug, silymarin.

Table 4. Effect of MEHA on Serum Total Bilirubin Levels

Group	Treatment	Total Bilirubin (mg/dL) Mean ± SEM
Group I	Isoniazid & rifampicin (200mg/kg, p.o)	0.72 ± 0.03
Group II	isoniazid (200 mg/kg, p.o), rifampicin (200 mg/kg, p.o) and Silymarin (100 mg/kg, p.o)	2.18 ± 0.07***
Group III	isoniazid (200 mg/kg, p.o), rifampicin (200 mg/kg, p.o) and MEHA (200 mg/kg, p.o)	0.86 ± 0.04###
Group IV	isoniazid (200 mg/kg, p.o), rifampicin (200 mg/kg, p.o) and MEHA (400 mg/kg, p.o)	1.36 ± 0.05**

Group V	Isoniazid & rifampicin (200mg/kg, p.o)	0.94 ± 0.03###

Values expressed as Mean ± SEM (n = 6), ***p < 0.001 vs normal control, **p < 0.01 vs disease control, ###p < 0.001 vs disease control



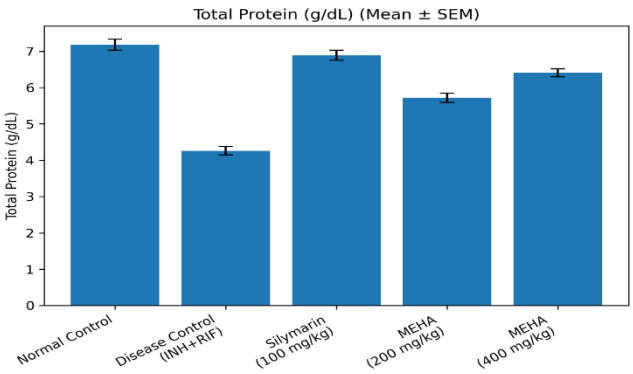
3.6 Effect of MEHA on Serum Total Protein Levels

Administration of isoniazid and rifampicin significantly reduced serum total protein levels in the disease control group compared with the normal control group, indicating impaired liver protein synthesis due to hepatic injury. Treatment with the methanolic extract of *Hedyotis aspera* (MEHA) significantly increased total protein levels in comparison with the disease control group. The improvement was dose-dependent, with the 400 mg/kg dose showing greater restoration of protein levels and an effect comparable to the standard drug silymarin, suggesting hepatoprotective activity.

Table 5. Effect of MEHA on Serum Total Protein Levels

Group	Treatment	Total Protein (g/dL) Mean ± SEM
Group I	Isoniazid & rifampicin (200mg/kg, p.o)	7.18 ± 0.15
Group II	isoniazid (200 mg/kg, p.o), rifampicin (200 mg/kg, p.o) and Silymarin (100 mg/kg, p.o)	4.26 ± 0.12***
Group III	isoniazid (200 mg/kg, p.o), rifampicin (200 mg/kg, p.o) and MEHA (200 mg/kg, p.o)	6.89 ± 0.14###
Group IV	isoniazid (200 mg/kg, p.o), rifampicin (200 mg/kg, p.o) and MEHA (400 mg/kg, p.o)	5.72 ± 0.13**
Group V	Isoniazid & rifampicin (200mg/kg, p.o)	6.41 ± 0.11###

Values are expressed as Mean ± SEM (n = 6), ***p < 0.001 vs normal control, **p < 0.01 vs disease control, ###p < 0.001 vs disease control



4. Histopathological Observations

Histopathological analysis of liver tissues from the disease control group revealed severe degeneration of hepatocytes, along with necrosis and fatty changes.

In contrast, rats treated with MEHA showed noticeable improvement in the liver structure, with reduced necrosis and partial restoration of normal hepatocyte architecture.

Figure-1: Photomicrograph of the liver tissue of normal group

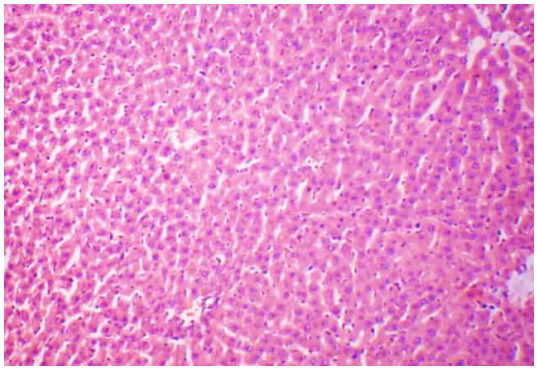


Figure-2: Photomicrograph of isoniazid and rifampicin the liver tissue treated group

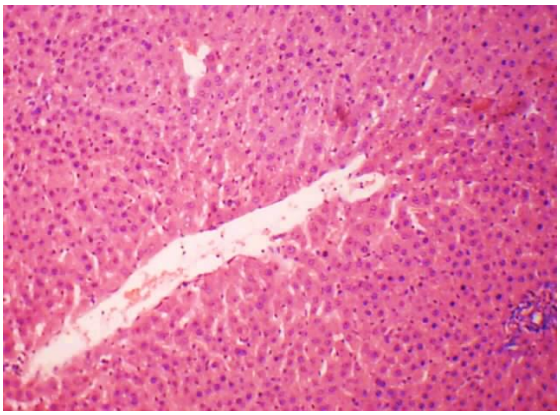


Figure-3: Photomicrograph of silymarin in the liver tissue treated group

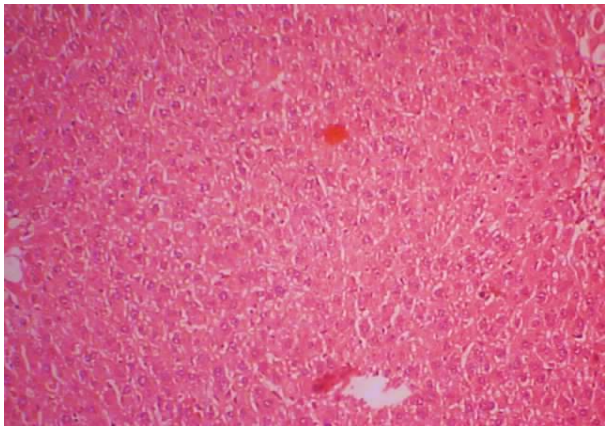


Figure-4: Photomicrograph the methanolic extract of *Hedyotis aspera* (200 mg/kg) in the liver tissue of treated group

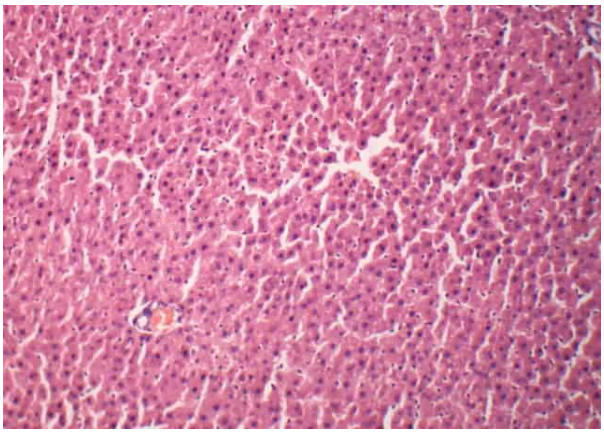
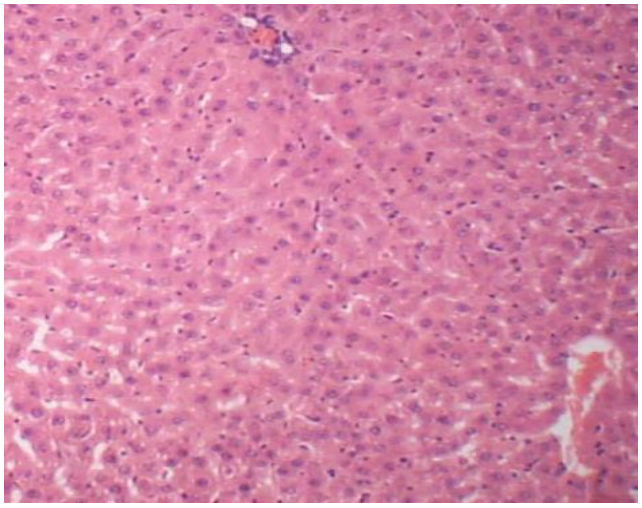


Figure-5: Photomicrograph of the methanolic extract of *Hedyotis aspera* (400 mg/kg) in the liver tissue treated group



5. Discussion

Drug-induced liver injury is a serious clinical concern and is frequently linked with the use of antitubercular medications such as isoniazid and rifampicin. These drugs can cause hepatotoxicity through the generation of harmful metabolites and increased oxidative stress, which ultimately leads to damage of liver cells and impairment of normal liver functions.

In the present investigation, administration of isoniazid and rifampicin caused a significant rise in the serum levels of SGOT, SGPT, ALP, and total bilirubin, along with a reduction in total protein levels. These changes clearly indicate severe liver damage. Increased transaminase levels generally reflect injury to hepatocyte membranes and the leakage of intracellular enzymes into the bloodstream, while elevated ALP and bilirubin levels suggest cholestatic damage to the liver. Treatment with the methanolic extract of *Hedyotis aspera* (MEHA) significantly lowered the elevated liver enzyme levels and bilirubin concentrations, while also restoring the reduced total protein levels. The hepatoprotective effect of the extract was dose-dependent, with the higher dose (400 mg/kg) showing greater improvement. The activity observed at this dose was comparable to that of the standard hepatoprotective drug, silymarin.

The biochemical findings were further supported by histopathological observations. Liver sections obtained from the disease control group exhibited clear signs of hepatocellular degeneration and necrosis. In contrast, liver tissues from the MEHA-treated groups showed noticeable improvement in hepatic structure with reduced cellular damage and partial restoration of normal architecture.

The hepatoprotective effect of *Hedyotis aspera* may be related to the presence of bioactive phytochemicals such as flavonoids and phenolic compounds. These compounds are known for their antioxidant properties, which help in protecting liver cells from oxidative stress and damage to cellular membranes.

6. Conclusion

The results of the present study indicate that the methanolic extract of *Hedyotis aspera* possesses significant hepatoprotective activity against isoniazid- and rifampicin-induced liver injury in experimental rats. The extract effectively lowered elevated liver enzyme levels, reduced bilirubin concentrations, and restored serum total protein levels. Histopathological findings also confirmed the protective effect of the extract on liver tissue structure.

Overall, these results suggest that *Hedyotis aspera* may have potential as a natural therapeutic agent for the management of drug-induced liver toxicity. However, additional studies are required to isolate and identify the active constituents responsible for this activity and to better understand the underlying mechanisms of hepatoprotection.

7. Limitations of the Study

Although the study demonstrated notable hepatoprotective activity of *Hedyotis aspera*, certain limitations should be considered. The evaluation mainly focused on biochemical and histopathological parameters, while detailed investigations involving molecular pathways and antioxidant markers were not performed. Moreover, the study used a crude methanolic extract, and the specific bioactive compounds responsible for the observed effects were not identified.

In addition, the experiment was carried out using an animal model, and therefore the findings may not be directly applicable to human clinical conditions. Further research involving phytochemical isolation, mechanistic studies, and clinical trials will be necessary to confirm the therapeutic potential of *Hedyotis aspera*.

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