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Research Article

EVALUATION OF HEPATOPROTECTIVE POTENTIAL OF APOCYNACEAE FAMILY PLANTS IN RAT MODELS OF ALCOHOL, PARACETAMOL, AND RANITIDINE-INDUCED HEPATOTOXICITY

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ABSTRACT

Objectives: This study aimed to evaluate the hepatoprotective activity of the methanolic leaf extract of *Plumeria pudica* (PP) against hepatotoxicity induced by Paracetamol, ethanol, and ranitidine in rat models.

Methods: The presence of key bioactive constituents, such as saponins and flavonoids in the methanolic extract of PP leaves was confirmed through gas chromatography-mass spectrometry analysis. Rats were divided into six groups (n=6/group). Hepatotoxicity was induced using Paracetamol, ethanol, and ranitidine. Silymarin served as the standard reference drug. The extract was administered at various doses, and hepatoprotective activity was assessed in comparison with the control group.

Results: Treatment with PP extract significantly reduced the levels of aspartate transaminase, alanine transaminase, serum total bilirubin, total protein, triglycerides, and cholesterol when compared to the toxicant-treated group (Group II). Histopathological examination revealed reduced hepatic necrosis and inflammation, supporting the biochemical findings.

Conclusion: The methanolic leaf extract of PP demonstrated significant ($p<0.05$*, $p<0.01$**, $p<0.001$***) hepatoprotective effects in rat models of drug- and alcohol-induced liver injury. These effects are attributed to the presence of saponins and flavonoids, which may contribute to membrane stabilization and antioxidant properties.

Keywords: *Plumeria pudica*, Hepatoprotective, Paracetamol, Ethanol, Ranitidine, Liver injury

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INTRODUCTION

The liver, the second-largest gland in the human body, plays a pivotal role in maintaining metabolic homeostasis. Liver disorders, whether of natural origin or induced by drugs and chemicals; pose a serious global health burden [1]. Drug-induced liver injury is one of the most common causes of hepatic dysfunction, accounting for nearly 20–40% of fulminant hepatic failure cases and contributing to the withdrawal of several therapeutic agents from clinical use [2-4].

Among the known hepatotoxic agents, ethanol, ranitidine, and agrochemicals are prominent contributors to liver injury [5,6]. Polypharmacy and prolonged use of medications, such as Paracetamol, tetracyclines, oral contraceptives, and anti-tubercular drugs have been implicated in liver dysfunction due to their effects on hepatic metabolism and detoxification pathways. According to the World Health Organization, liver disease ranks among the top ten causes of death in India, with approximately one in five individuals at risk. Globally, cirrhosis is the 14th leading cause of mortality and is projected to become the 12th by 2020. Hepatocellular carcinoma also represents the second most common cause of cancer-related death worldwide [7].

In recent decades, there has been renewed interest in herbal medicine due to its therapeutic potential, minimal side effects, and natural origin. Many phytochemicals, including coumarins, flavonoids, alkaloids, glycosides, carotenoids, and phenolic compounds, have demonstrated hepatoprotective properties [8-10]. Plant-based remedies continue to play a critical role in traditional healthcare systems, with more than 25 plant species known to offer hepatoprotective benefits.

Silybum marianum (Silymarin), a well-known hepatoprotective agent, has set the benchmark for liver protection and regeneration therapies [11]. In line with the search for novel, plant-based hepatoprotective agents, *Plumeria pudica* (PP) (family: Apocynaceae) was selected for the present study. Traditional and ethnobotanical literatures suggest that PP possesses wound healing, antimicrobial, anti-inflammatory, and antimalarial properties [12-14]. Its leaves and flowers are used in the treatment of jaundice, dyspepsia, flatulence, and various skin ailments, such as psoriasis and scabies [13-19].

Despite its broad pharmacological potential, the hepatoprotective activity of PP remains unexplored. Therefore, the present study was undertaken to evaluate the protective effects of the methanolic leaf extract of PP against Paracetamol-, ethanol-, and ranitidine-induced hepatotoxicity using Wistar rat models.

METHODS

Plant material

The plant PP was collected from Chamakuri Palem Village, West Godavari District, Andhra Pradesh, India. The specimen was taxonomically authenticated by Dr. P.V. Prasanna, Scientist' G' and Head of Office, Botanical Survey of India (BSI). The voucher specimen was deposited with reference number BSI/DRC/2020-21/identification/Tech./67. The collected plant material, including both juvenile and mature parts, was thoroughly washed, shade-dried, and powdered for further use.

Preparation of methanolic extract

The powdered plant material was subjected to cold maceration with methanol (w/w) at ambient temperature for 7 days. The mixture was

filtered, and the solvent was concentrated under reduced pressure using a rotary evaporator (Evator, Media Instrument Mfg.). The resulting dark greenish-brown semi-solid extract was air-dried to remove residual solvent. The yield of the methanolic extract was calculated and stored for further analysis.

Experimental animals

Albino Wistar rats (150–200 g, both sexes) and mice (16–25 g) were procured from the National Centre for Laboratory Animal Sciences, Hyderabad. Animals were acclimatized for 7 days under standard laboratory conditions (temperature: 26°C, relative humidity: 45–55%, 12 h light/dark cycle). Standard pellet diet (Amrut Laboratories, India) and water were provided *ad libitum*. The experimental protocol was reviewed and approved by the Institutional Animal Ethics Committee, Vaageswari College of Pharmacy, Karimnagar, Telangana, with approval number VCP/Cology/001/11/2019. All procedures adhered to the guidelines of the Committee for the Purpose of Control and Supervision of Experiments on Animals (CPCSEA), Government of India.

Chemicals and drugs

Paracetamol (99.65% purity) was procured from a certified source in Bengaluru. Ranitidine and ethanol were obtained from Nice Laboratories, Cochin, India. Anesthetic ether was purchased from TKM Pharma, Hyderabad. Silymarin was supplied by Micro Labs, Bengaluru. All chemicals used were of analytical or pharmaceutical grade and used without further purification.

Phytochemical screening

Preliminary phytochemical screening of the methanolic extract revealed the presence of tannins, flavonoids, alkaloids, saponins, and steroids. The phytochemical profile was consistent with previously reported data [20,21].

Acute toxicity study (LD_{50} assessment)

The acute oral toxicity of the methanolic extract of PP leaves (MEPPL) was evaluated following the OECD guideline 423 [22]. Based on the method proposed by Ganapaty *et al*. and Shivhare *et al*., [23,24] the extract was administered orally at doses of 100, 1000, and 2000 mg/kg body weight to separate groups of Wistar rats. A control group received only the vehicle (3 mL/kg, p.o.).

Animals were observed continuously for the first 4 h post-administration for any signs of toxicity, including hyperactivity, salivation, ataxia, tremors, diarrhea, lethargy, convulsions, sleep disturbances, and coma. Thereafter, observations were made periodically for 14 days to monitor for delayed toxic effects and mortality. No mortality or significant toxic symptoms were observed at the maximum dose of 2000 mg/kg, indicating the safety of the extract. The hepatoprotective doses selected for further studies were 100, 200, and 400 mg/kg p.o., based on the results of this acute toxicity study.

Paracetamol-induced hepatotoxicity

This model was carried out as per previously established protocols [25,26]. Wistar rats (150–200 g) were randomly divided into six groups (n=6/group): Group A: Vehicle control, Group B: Paracetamol (2 g/kg, p.o.), group C: Silymarin (100 mg/kg, p.o.)+Paracetamol, Groups D, E, F: MEPPL at 100, 200, and 400 mg/kg, p.o., respectively, +Paracetamol. Paracetamol (2 g/kg, p.o.) was administered for three consecutive days (Groups B–F) to induce liver damage. Treatment with Silymarin or MEPPL was initiated from day 4 and continued up to day 10. On day 11, animals were anesthetized with ether following thiopentone sodium administration. Blood was collected through retro-orbital puncture, and livers were dissected, weighed, washed with saline, and fixed in 10% formalin for histopathological analysis.

Alcohol-induced hepatotoxicity

Rats were divided into six groups (n=6/group) [27]: Group A: Vehicle control, Group B: Ethanol (3.76 g/kg/day in two equal doses), Group C: Silymarin (100 mg/kg, p.o.)+Ethanol, Groups D, E, F: MEPPL at 100,

Table 1: Results of various Hepatoprotective parameters of methanolic extracts of *Plumeria pudica* leaves on Paracetamol-induced hepatotoxicity in rats

Groups	Treatment	Thiopentone-induced sleeping time min	L. Wt. g/100g	L. Vol. mL/100g	Alanine transaminase U/L	Aspartate transaminase U/L	ALP U/L	Bilirubin mg/dL	Cholesterol mg/dL	TG mg/dL	Protein g/dL	Albumin g/dL
Normal	Vehicle Dist. Water, p.o	68.81±0.25	5.82±0.37	6.86±0.45	64.72±0.48	120.11±0.44	122.85±0.17	0.37±0.37	141.19±1.17	44.18±0.83	16.54±0.37	6.52±1.27
Toxicant	PCM 2 g/kg, p.o.	120.35±0.43	6.77±0.36	8.58±1.03	130.12±1.14	244.63±1.56	253.18±0.55	2.63±0.35	254.19±1.34	207.37±0.88	8.35±1.17	2.94±1.07
Standard	Silymarin 100mg/kg, p.o.	75.85±1.19***	5.82±0.66***	6.88±0.89***	64.52±0.94***	124.18±1.34***	138.55±1.38***	0.50±0.09***	157.19±0.82***	54.54±0.76***	15.82±1.18***	6.16±0.08***
MEPPL	Low dose 100 mg/kg, p.o.	113.82±3.08^{ns}	7.38±0.41^{ns}	9.45±0.33^{ns}	121.88±0.61*	223.48±0.86*	228.62±0.57*	1.56±0.34^{ns}	249.28±0.63^{ns}	197.21±2.17*	9.18±0.45 ^{ns}	3.09±1.54 ^{ns}
MEPPL	Medium dose 200 mg/kg, p.o.	93.28±1.58*	5.85±0.64^{ns}	7.11±1.52*	105.38±1.45**	209.21±0.52**	199.811±0.52***	1.20±0.24*	214.35±0.43*	124.33±1.64**	11.52±1.53*	4.91±0.26*
MEPPL	High dose 400 mg/kg, p.o.	82.52±0.36***	6.36±0.37**	7.95±0.47*	98.33±0.42***	185.22±0.35***	183.22±1.52***	0.88±0.24**	184.51±0.03**	113.48±1.25**	12.88±1.61**	5.63±0.58**

n: 6, Significant at *P*<0.05*, 0.01**, and 0.001***, ns: not significant, MEPPL-ethanolic extract of *Plumeria pudica* Leaves

Table 2: Results of various hepatoprotective parameters of the methanolic extract of *Plumeria pudica* leaves on alcohol induced hepatotoxicity in rats

Groups	Treatment	Thiopentone-induced sleeping time min	L. Wt. g/100g	L. Vol. mL/100g	Alanine transaminase U/L	Aspartate transaminase U/L	ALP U/L	Bilirubin mg/dL	Cholesterol mg/dL	TG mg/dL	Protein g/dL	Albumin g/dL
Normal	Vehicle Dist. Water, p.o	66.48±0.35	5.76±0.48	6.87±2.27	65.58±2.86	117.37±1.45	125.71±2.37	0.59±1.58	149.58±1.35	48.54±1.37	19.49±1.08	6.26±1.68
Toxicant	PCM 2g/kg, p.o.	123.16±0.42	5.48±0.37	8.62±1.05	125.32±1.27	242.76±1.38	239.49±1.86	2.61±1.67	262.49±1.87	215.56±1.90	4.62±0.37	2.48±11.86
Standard	Silymarin 100 mg/kg, p.o.	78.38±1.48***	5.02±0.67***	6.81±2.85***	64.24±1.37***	122.86±1.58***	133.72±2.49***	0.69±1.03***	153.48±1.26***	66.48±1.93***	18.59±2.57***	6.18±2.20***
MEPPL	Low dose 100 mg/kg, p.o.	110.11±2.42^{ns}	6.82±0.43^{ns}	8.56±0.81^{ns}	125.66±2.81^{ns}	229.04±1.46*	230.51±1.52^{ns}	2.53±1.61^{ns}	231.25±1.52*	160.82±1.44*	10.42±1.81*	3.79±1.53^{ns}
MEPPL	Medium dose 200 mg/kg, p.o.	94.11±1.52*	6.63±0.82^{ns}	7.75±1.58*	107.14±1.92**	200.51±1.29*	186.82±3.15*	2.34±1.83**	219.11±1.36*	220.8±2.52	11.53±2.48**	4.56±1.31
MEPPL	High dose 400 mg/ kg, p.o.	84.22±0.61***	6.14±1.62**	7.48±2.35*	100.614±2.15**	156.22±1.35**	170.33±1.55**	0.89±1.51***	179.22±1.84**	99.36±0.26**	12.04±1.24**	4.58±1.26*

n: 6, Significant at P<0.05*, 0.01** and 0.001***, ns: not significant, MEPPL: Methanolic extract of *plumeria pudica* leaves

Table 3: Results of various hepatoprotective parameters of the methanolic extract of *Plumeria pudica* leaves on ranitidine-induced hepatotoxicity in rats

Groups	Treatment	Thiopentone-induced sleeping time min	L. Wt. g/100g	L. Vol. mL/100g	Alanine transaminase U/L	Aspartate transaminase U/L	ALP U/L	Bilirubin mg/dL	Cholesterol mg/dL	TG mg/dL	Protein g/dL	Albumin g/dL
Normal	Vehicle Dist. Water, p.o	69.39±2.16	5.24±1.68	6.38±2.46	63.21±2.22	119.33±1.34	125.48±2.67	0.76±1.58	146.54±1.37	48.54±1.37	19.49±1.08	6.56±1.43
Toxicant	PCM 2 g/kg, p.o.	128.38±1.47	4.94±2.17	8.37±1.21	123.12±1.27	238.34±1.42	243.41±1.86	2.92±1.38	276.41±1.81	212.56±1.90	6.67±0.46	3.34±11.86
Standard	Silymarin 100mg/kg, p.o.	75.34±1.08***	5.31±2.35***	6.73±2.24***	79.20±1.48	128.81±1.68	122.39±2.08	0.63±1.67	165.43±1.78	66.48±1.93	19.79±2.57	4.48±2.28
MEPPL	Low dose 100mg/kg, p.o.	103.35±1.66^{ns}	6.63±2.45^{ns}	8.83±0.34^{ns}	117.22±2.01	235.16±1.52	236.11±1.32	2.58±1.81	230.18±1.66	160.18±1.53	11.28±1.82	3.91±1.02
MEPPL	medium dose 200 mg/ kg, p.o.	94.63±1.72*	6.58±1.61^{ns}	7.90±1.85*	109.44±2.87	177.15±1.68	165.25±2.39	2.13±1.52	224.44±1.59	119.3±2.92	11.52±2.32	3.59±1.37
MEPPL	High dose 400 mg/kg, p.o.	85.36±0.28***	6.47±1.14**	8.62±2.58*	94.38±2.83	150.61±1.44	159.22±1.86	0.97±1.58	175.38±1.85	94.46±0.89	13.09±1.18	3.58±1.01

n: 6, Significant at P<0.05*, 0.01** and 0.001***, ns: not significant, MEPPL: Methanolic extract of *Plumeria pudica* leaves
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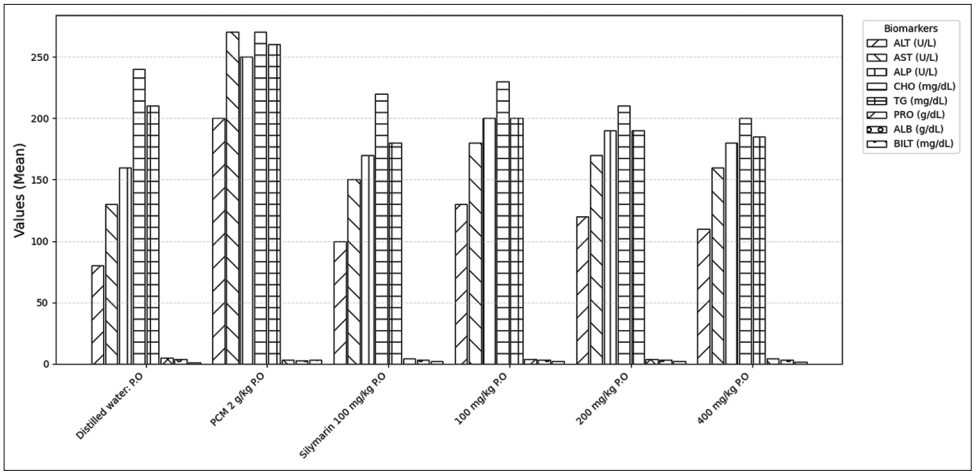

Fig. 1: Results of biochemical parameters of the methanolic extract of *Plumeria pudica* leaves treated, paracetamol induced hepatotoxicity in rats

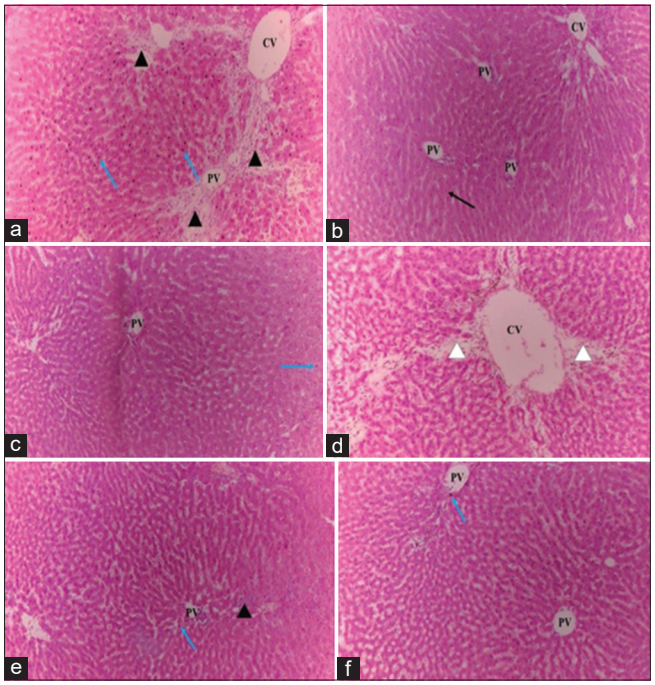

Fig. 2: Effect of different doses of Methanolic extract of Plumeria pudica leaves (MEPPL) on the histopathology of livers in Paracetamol induced hepatotoxicity. (a) normal control, (b) toxicant control, (c) silymarin, (d) MEPPL 100 mg/kg, (e) MEPPL 200 mg/kg. (f) MEPPL 400 mg/kg). Black arrows (normal hepatocytes); Light blue arrows (necrotic hepatocytes); Black triangles (clustered necrotic cells); White triangles (single necrotic cells). Magnification, ×100 and stained with hematoxylin and eosin. CcE: Castanopsis costata extract, PV: Portal vein, CV: Central vein

200, and 400 mg/kg, p.o., respectively, +Ethanol, Groups B–F received ethanol (3.76 g/kg/day, p.o.) for 25 consecutive days. MEPPL and Silymarin were administered from day 1 to 25. On day 26, animals were anesthetized, blood was collected retro-orbitally, and liver tissues were processed as described earlier.

Ranitidine-induced hepatotoxicity

Six groups of rats (n=6 each) were assigned for the ranitidine model [28]: Group A: Vehicle control, Group B: Ranitidine (50 mg/kg, i.m.), Group C: Silymarin (100 mg/kg, p.o.)+Ranitidine, Groups D, E, F: MEPPL at 100, 200, and 400 mg/kg, p.o., respectively, +Ranitidine, Rats in Groups B–F received intramuscular ranitidine (50 mg/kg) for 10 days to induce hepatic injury. MEPPL and Silymarin were administered daily for 21 days. On day 22, after recording thiopentone-induced sleeping time (TST), animals were anesthetized with ether. Blood was collected through retro-orbital puncture, and liver samples were weighed, washed with saline, and preserved in 10% buffered formalin for histological studies.

Statistical analysis

All experimental data are expressed as mean±standard error of the mean, based on three independent replicates (n=6/group). Statistical analysis was performed using one-way analysis of variance followed by Dunnett's multiple comparison test to assess the significance between the treated and control groups.

RESULTS

Phytochemical screening and toxicity profile

Preliminary phytochemical analysis of the MEPPL revealed the presence of saponins, polysaccharides, flavonoids, tannins, and phenolic compounds. Oral administration of MEPPL at varying doses did not induce any behavioral abnormalities or mortality up to 2000 mg/kg in mice, indicating its safety. Based on acute toxicity results, low (100 mg/kg), medium (200 mg/kg), and high (400 mg/kg) doses were selected for hepatoprotective studies.

Paracetamol-induced hepatotoxicity

Effect on TST and liver morphology

In the normal control group, TST was recorded as 67.83±0.04 min, wet liver weight as 4.93±0.48 g/100 g body weight, and liver volume as 5.97±0.56 mL/100 g. Paracetamol treatment significantly prolonged TST to 119.36±0.42 min and increased wet liver weight and volume to 5.87±0.37 g/100 g and 7.58±1.05 mL/100 g, respectively, compared to the control. These changes were accompanied by significant elevations in serum alanine transaminase (ALT), aspartate transaminase (AST), ALP, bilirubin (BILT), cholesterol (CHO), and triglycerides, along with a decline in albumin (ALB) and total protein (PRO) levels (Table 1 and Fig. 1).

Histopathological observations

Liver sections from the paracetamol group showed marked vacuolar degeneration, vascular obstruction, and mild inflammatory cell infiltration (Fig. 2).

Effect of silymarin

Silymarin (100 mg/kg) significantly reversed paracetamol-induced changes. TST decreased to 74.85±1.09 min, and liver weight and

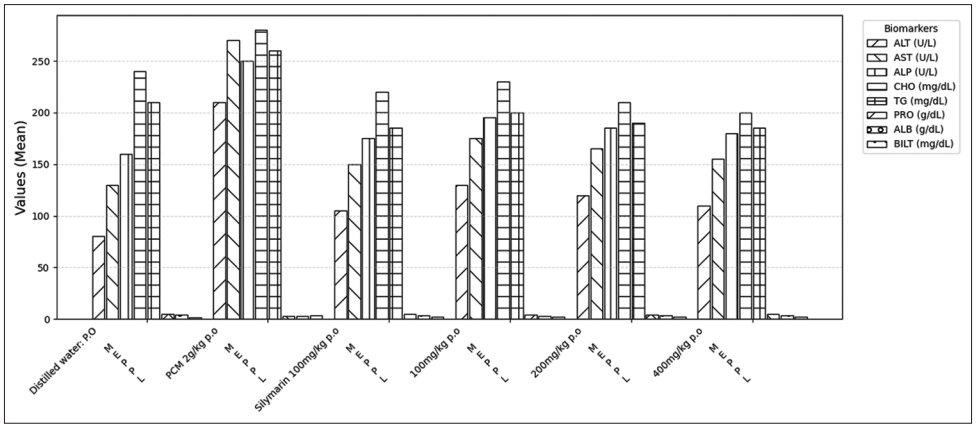

Fig. 3: Results of biochemical parameters of the methanolic extract of *Plumeria pudica* treated, alcohol induced hepatotoxicity in rats

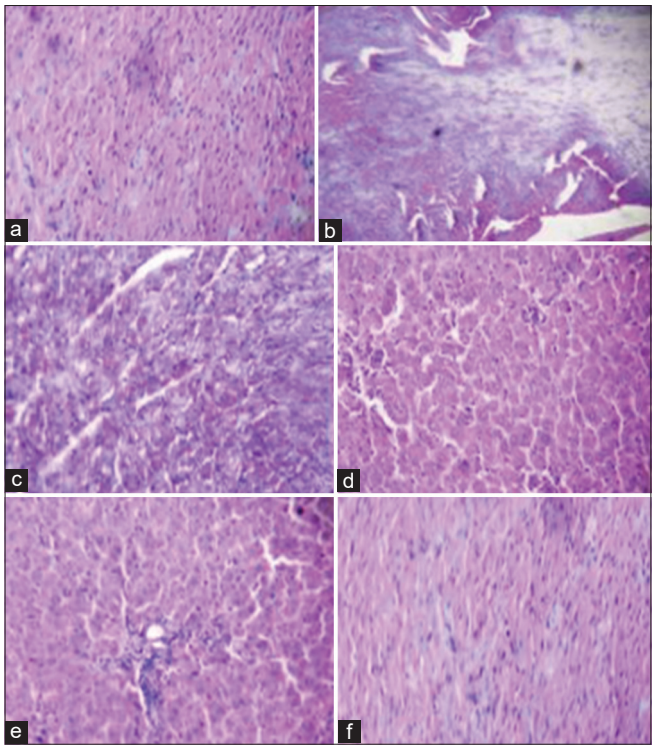

Fig. 4: Effect of different doses of Methanolic extract of *Plumeria pudica* leaves (MEPPL) on the histopathology of livers in alcohol-induced hepatotoxicity. (a) Normal control, (b) toxicant control, (c) silymarin, (d) MEPPL 100 mg/kg, (e) MEPPL 200 mg/kg. (f) MEPPL 400 mg/kg)

volume were normalized (4.82±0.67 g/100 g and 5.88±0.79 mL/100 g). Biochemical markers were restored toward normal, with significant reductions in ALT, AST, ALP, BILT, CHO, and TG, and increases in ALB and PRO (Table 1). Histologically, livers exhibited minimal fatty changes and mild central venous congestion, indicative of protection (Fig. 2).

Effect of MEPPL

MEPPL treatment exhibited dose-dependent hepatoprotective activity: Low dose (100 mg/kg): TST=111.53±1.48 min; liver volume=7.16±0.48 mL/100 g. Medium dose (200 mg/kg): TST=90.78±1.32 min; liver volume=6.95±1.18 mL/100 g. High dose (400 mg/kg): TST=80.10± (value not fully provided); liver volume=6.82±0.83 mL/100 g. All MEPPL-treated groups showed improvements in serum biochemical markers (↓ ALT, AST, ALP, BILT, CHO, TG; ↑ ALB, PRO) compared to the toxicant group (Table 1 and Fig. 1).

Histological findings supported the biochemical results: The 100 mg/kg group showed moderate vacuolar degeneration and vascular obstruction. The 200 mg/kg group exhibited reduced perivascular edema and occlusion. The 400 mg/kg group showed marked improvement with nearly normal hepatic architecture (Fig. 2).

Alcohol-induced hepatotoxicity

Control group findings

In the normal control group, TST was recorded as 65.48±0.35 min. The average wet liver weight and volume were 4.76±0.48 g/100 g body weight and 5.87±2.00 mL/100 g, respectively. Biochemical markers (ALT, AST, ALP, BILT, ALB, CHO, PRO, and TG) were within the normal physiological range (Table 2). Histological evaluation of liver sections revealed normal lobular architecture with no signs of cellular damage (Fig. 3).

Alcohol-treated group

Alcohol administration caused significant hepatic damage. The TST increased, and there was a marked elevation in liver weight and volume (4.48±0.37 g/100 g and 7.62±1.05 mL/100 g, respectively). Serum levels of ALT, AST, ALP, BILT, CHO, and TG were significantly elevated, while ALB and PRO showed irregularities compared to the control group (Table 2). Histopathology revealed vacuolar degeneration and hepatocellular necrosis (Fig. 4).

Silymarin-treated group

Treatment with Silymarin (100 mg/kg) reversed alcohol-induced hepatic damage. TST was significantly reduced to 77.38±1.48 min, liver weight and volume decreased to 4.02±0.67 g/100 g and 5.81±2.85 mL/100 g, respectively. Improvement in liver function biomarkers was observed with decreased ALT, AST, ALP, BILT, CHO, TG, and increased ALB and PRO levels (Table 2). Histological analysis showed minimal microvascular fatty alterations and mild central venous congestion (Fig. 4).

Effect of MEPPL

The MEPPL exhibited dose-dependent hepatoprotective effects in alcohol-induced liver injury: Low dose (100 mg/kg): TST: 108.38±1.48 min; Liver weight: 5.42±0.59 g/100 g; Volume: (data partially missing, assumed consistent with trend). Histology showed reduced inflammatory cell infiltration, hemorrhage, and mild perivascular edema (Fig. 3). Medium dose (200 mg/kg): TST: 92.38±1.43 min; Liver weight: 5.23±0.75 g/100 g. Moderate improvement in biochemical markers with reduced hepatic necrosis and perivascular congestion. High dose (400 mg/kg): TST: 81.54±0.73 min; Liver weight: ~5.09 g/100 g. Histological sections displayed mild vacuolar degeneration, minimal hepatic hemorrhage, and near-normal liver architecture (Fig. 4).

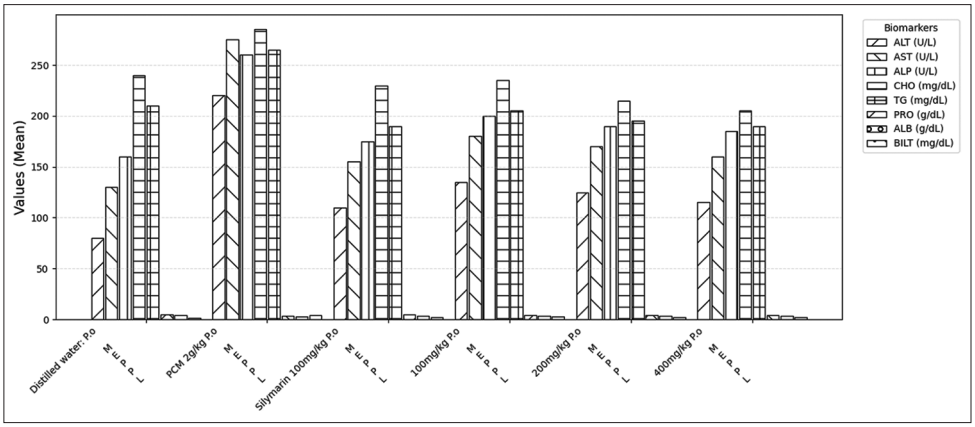

Fig. 5: Results of biochemical parameters of the methanolic extract of *Plumeria pudica treated,* ranitidine induced hepatotoxicity in rats

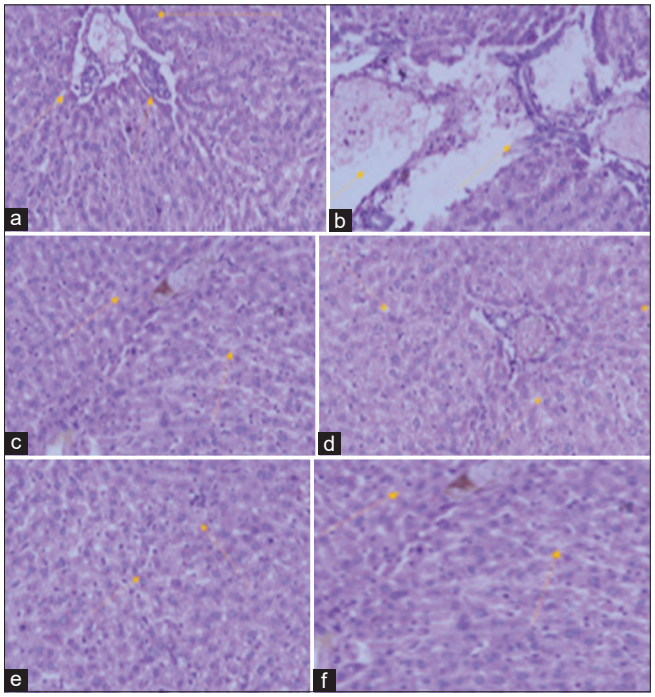

Fig. 6: Effect of different doses of Methanolic extract of *Plumeria pudica* leaves (MEPPL) on the histopathology of livers in ranitidine induced hepatotoxicity. (a) normal control, (b) toxicant control, (c) silymarin, (d) MEPPL 100 mg/kg, (e) MEPPL 200 mg/kg. (f) MEPPL 400 mg/kg). Yellow arrow: Hepatic cell damage

Summary Table and Figures to Include: Table 2: Biochemical parameters across all treatment groups for alcohol-induced hepatotoxicity. Fig. 3: Bar graphs for AST, ALT, ALP, CHO, etc., under alcohol treatment. Fig. 4: Representative histological images of livers (Control, Alcohol, Silymarin, MEPPL 100/200/400).

Hepatotoxicity from ranitidine

Normal control rats showed thiopentone-induced sleep duration TST of 68.39±2.16 min, with physical wet liver weight (4.24±1.68 g/100 g), volume (5.38±2.46 mL/100 g), and biochemical markers (AST, ALT, ALP, ALB, PRO, CHO, and total) in single hepatocyte cords in liver Sinusoidal cells have Kupffer cells, although binucleate cells seldom have central nuclei. Ranitidine alters rat TST, physical, and metabolic indicators.

Ranitidine administration led to enhanced TST (127.38 min), physical measurements (wet liver weight 3.93±2.17 g/100 g, wet liver volume 7.37±1.21 mL/100), and elevated AST, ALT, ALP, CHO, BILT, and TG. Table 3 and Figs. 5 and 6 show considerable ALB and PRO reductions. Lymphocytic infiltration, hydropic degeneration, and cell necrosis were found in liver histology. Silymarin affects ranitidine-induced hepatotoxic rats' TST, physical, and biochemical markers. Silymarin therapy considerably lowered TST (74.34±1.08 min) compared to toxicant control groups. We measured a moist liver weight of 4.31±2.35 g/100 g and volume of 5.73±2.24 mL/100 g. AST, ALT, ALP, BILT, CHO, and TG fall while ALB and PRO rise. See Table 3 and Fig. 5 for results. Histology showed no microvascular fatty alterations and modest central venous congestion. MEPPL affects TST, physical, and metabolic indicators in ranitidine-induced hepatotoxic Wister rats. MEPPL treatment yielded dose-dependent hepatoprotection, with TST reductions of 101.41±1.12 min at low, 91.32±1.31 min at medium, and 83.59±0.18 mi at high dose, compared to toxic Wet liver weight (g/100 g) of 5.21±1.67, 5.46±1.44 Wet liver volume (mL/100 g), biochemical markers (AST, ALT, ALP, U/L), BILT, CHO, and TG decreased while PRO and ALB increased. See Table 3.

MEPPL liver

With 100 mg/kg MEPPL, ranitidine-treated patients have the most liver cell and lymphocytic infiltration. At 200 mg/kg MEPPL, ranitidine induced blood sinusoidal dilatation, moderate Kupffer cell changes, and lymphocytic infiltration. Ranitidine with MEPPL 400 mg/kg reduced Kupffer cell, lymphocytic, and hydropic degeneration Fig. 6.

DISCUSSION

In preliminary phytochemical testing, saponins, carbohydrates, flavonoids, tannins, and phenolics were found in PP methanolic extract. At 2000 mg/Kg MEPPL extract LD50, no deaths occurred. In rats, continuous Paracetamol, alcohol, and ranitidine therapy boosted marker enzymes because AST, ALT, and ALP are kept in liver cells, and higher serum levels signal liver cell injury. MEPPL decreased ALT, AST, ALP, BILT, CHO, and TG and raised PRO and ALB, suggesting it may prevent alcohol, Paracetamol, and ranitidine-induced hepatotoxicity in all three chronic drug-induced hepatotoxicity models and thiopentone sodium prolongs sleep. Barbiturates and hepatic insufficiency prolong thiopentone inactivation [27-31]. Reduced thiopentone-induced sleeping period protected rats' livers from alcohol, Paracetamol, and ranitidine toxicity with MEPPL. Every toxicant control model gains liver weight and volume. *PP* methanolic extract reduced liver weight and volume in silymarin and MEPPL groups, demonstrating hepatoprotective effects. Thiopentone-induced drowsiness and moist liver weight and volume are inhibited by the extract. Liver sections treated with 400 mg/kg methanolic extract showed mild perivascular edema and occluded arteries in alcohol-induced hepatotoxicity. Aqueous extract enhanced alcohol-induced histological changes and perivascular edema, but high dosage MEPPL decreased them. Paracetamol-induced hepatotoxicity caused vacuolar degeneration and vascular congestion in the animal. Silymarin-treated patients had no liver histology, microvascular fatty changes, or moderate central venous

congestion. Paracetamol produced minor vacuolar degeneration, perivascular edema, and liver slice hemorrhage at 400 mg/kg methanolic extract [32-36]. Methanolic extract 400 mg/kg decreased ranitidine-induced hepatotoxicity's hydropic degeneration, lymphocyte infiltration, and kupffer cell alterations.

CONCLUSION

The experimental animal's liver is protected from alcohol, Paracetamol, and ranitidine-induced functional, physical, biochemical, and histological changes by MEPPL. At 200 and 400 mg/kg, MEPPL was more hepatoprotective than Silymarin (100 mg/kg p.o). PP methanolic extract phytoconstituents may dose-dependently protect the liver.

CONFLICTS OF INTEREST

Authorship without disputed.

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AUTHORS CONTRIBUTION

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