



Full Length Article



Hepatoprotective activity of *Peltophorum pterocarpum* leaf and bark in the isoniazid and rifampicin-induced hepatotoxic rats

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ABSTRACT

Background: In recent years, various phytomedicines have been used in the treatment of hepatic disorders. The aim of this study is to find out whether *Peltophorum pterocarpum* bark and leaves can help rats that have been exposed to isoniazid and rifampicin-induced hepatotoxicity.

Materials and Methods: The rats were divided into 10 groups each with 6 rats. The liver damage is induced by isoniazid and rifampicin. The leaf and bark of *P. pterocarpum* extracted with ethanol are freshly mixed in sterile water (100, 200 and 400 mg/kg body weight), and given to rats orally in the early morning as a single dosage per day until the study period. The animals were sacrificed and the tissue and serum samples were collected for further investigations.

Results: The liver damage induced by isoniazid and rifampicin altered the various biochemical parameters levels, but after the treatment of *P. pterocarpum* barks and leaves the levels were significantly altered when compared to the negative control rats. The drug silymarin was used as a standard.

Conclusion: The extracts have the protective effect of liver markers and membrane-bound enzymes against the toxin-treated rats. This result highlights the hepatoprotective properties of the leaves and barks of the plant in a similar manner and the formulation (Group 10) have high beneficial effects than other groups.

1. Introduction

Hepatic diseases are the most serious ailments including acute hepatitis, chronic hepatitis, hepatosis and cirrhosis. It is caused due to hepatotoxic agents, high consumption of alcohol, infections and auto-immune disorders. The improper or non-functional condition in the liver is caused by liver damage in which the majority of the liver cells die or turn to the fibrotic stage. In this condition the therapy can be considered, which would boost the growth of the liver cells, to retrieve the damaged cells into the normal cells (Kamble et al., 2008). The use of natural and herbal medicines to treat a wide range of serious illnesses that are currently plaguing people all over the world is becoming more and more

popular. Many commercial medications are taken off the market due to their serious side effects and expensive cost. This is especially the case for their hepatotoxic adverse effects. As a result of this, a wide range of polyherbal formulations are currently advised for the management of several chronic illnesses, like, cancer, hypertension, heart disease, liver problems, and others.

Peltophorum pterocarpum is a well-known ornamental tree that grows along roadsides and is a member of the *Fabaceae* family. For their therapeutic benefits, including those that are neuroprotective and memory enhancing, antibacterial, anti-diabetic, cardiotoxic, antioxidant, anti-inflammatory, hypocholesterolemic, anti-arthritis, and anti-cancer, all of the plant's parts have ethnobotanical and scientific

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records (Devi and Battu, 2018). Phenolic acids, flavonoids, terpenoids, alkaloids, steroids, carotenoids, tannins, monoterpenes, hexadecanoic acid, octadecanoic acid, saponins, etc., were found to be distributed in the plant, according to phytochemical studies (Amala and Poonguzhali, 2015). The *P. pterocarpum* was found to contain phenolic acids, flavonoids, tannins, saponins, coumarins, carotenoids, octadecanoic acid, β -sitosterol, [2–4] (-)-epicatechol, valeronone, isosativene, hexadecanoic acid, octadecanoic acid, steroids, alkaloids, amino acids, carotenoids, coumarins, (+)-leucocynidin, quercetin, berginin, vitamins, etc. (Jain et al., 2012). The leaves and blossoms are employed to treat skin problems, sleeplessness, sprains, swellings, muscular pains and intestinal complaints behind pain during childbirth and are also comprehended to be acceptable sleep inducers (Jash et al., 2014). The goal of this investigation is to evaluate the beneficial hepatoprotective efficiency of bark and leaves of *P. pterocarpum* in rats intoxicated with isoniazid and rifampicin.

2. Materials and methods

2.1. Collection of plants and extraction

The *P. pterocarpum* barks and leaves were obtained from Tiruchirappalli, India, during the month of March to July. The plant specimen was recognized and placed at the Rapinat Herbarium, St. Joseph's College, Tiruchirappalli, India. The traditional method was used for preparing ethanolic extract from the plant. The barks and leaves were dried in the shade and powdered mechanically then the Soxhlet apparatus was used to prepare the extract using ethanol. The filtrate obtained was dehydrated in a vacuum and then the extracts were stored at a cold temperature till further use.

2.2. Experimental design

The Wistar rats (adult male, 56 days old, and 150–165 g weight) were procured and maintained at 25°C with 12 h of alternative cycles of light and dark. The pellets were balanced with all essential nutrients and *ad libitum* water was given. For conducting the experimental protocols and handling of animals were authorized by the Institutional Animal Ethics Committee, Srimad Andavan College of Arts and Science, Tiruchirappalli, India (Registration Number: SAC/IAEC/BC/2016-/Ph.D.-007).

Every day during the experimental period, rats were given a single oral dosage of plant extracts (ethanolic extract) in the early morning. Animals used in experiments were distributed randomly into 10 groups and each group contained six rats housed individually. All the experimental animals were intoxicated with isoniazid and rifampicin except for the control group. Animals classified as control (G1) were given basal diet, negative control (G2) Intoxicated with isoniazid and rifampicin (untreated), G2 treated with *P. pterocarpum* (leaf extract) of 100 mg/kg (G3), G2 treated with *P. pterocarpum* (leaf extract) of 200 mg/kg (G4), G2 treated with *P. pterocarpum* (leaf extract) of 400 mg/kg (G5), G2 treated with *P. pterocarpum* (bark extract) of 100 mg/kg (G6), G2 treated with *P. pterocarpum* (bark extract) of 200 mg/kg (G7), G2 treated with *P. pterocarpum* (bark extract) of 400 mg/kg (G8), silymarin of 25 mg/kg and G2 administered with both extract (G10).

2.3. Analysis of the tissue and serum samples

Following the completion of the investigation period, the animals were fasted overnight for about 12 h and the samples were collected from treated rats by sacrificing them with standard protocol. The collected samples were tested for the following parameters of membrane-bound enzymes including, liver biomarkers like creatine kinase (CK), gamma glutaryl transferase (GGT), lactate dehydrogenase (LDH) and lipase and Na^+K^+ ATPase, Mg^{2+} ATPase, Ca^{2+} ATPase, total bilirubin and direct bilirubin in Turbo Chem 100 biochemical analyzer

with commercially available kits from CPC Diagnostics.

2.4. Tissue sampling for histopathological study

For histopathological study, three rats from each group were perfused with cold physiological saline, followed by formalin (10% formaldehyde). The liver was excised immediately and fixed in 10% formalin. The classical paraffin sectioning, and haematoxylin eosin staining techniques were used for histopathological studies followed by (Slaoui and Fiette, 2011).

2.5. Statistical analysis

The results obtained from the biochemical analysis were statistically evaluated using one-way ANOVA followed by DMRT (Duncan's multiple range tests) using SPSS software 17 (Chicago, USA). The values given in the table are mean \pm SD (standard deviation). $P < 0.05$ was considered statistically significant.

3. Result

The group intoxicated with isoniazid and rifampicin showed a reduction in body and liver weights. Table 1 represents the changes in the weight of the liver and body in experimental groups. Rats in all the groups except for the control showed a reduction in their body and liver weights. A steady increase in body weight was noted in the groups treated with ethanolic extract of *P. pterocarpum* leaves and barks and the results were compared to the silymarin-treated rats. Compared to the control, rats which received standard drug didn't show an increase in body weight.

Table 2 represents the results of LDH, GGT, lipase and CK. Increases in levels of LDH, GGT, lipase and CK were observed in groups induced with isoniazid and rifampicin. After the treatment with plant extracts and standard drug, the concentrations were normalized in the rats. Table 3 represents the levels of liver protein, direct bilirubin and total bilirubin in control and experimental rats. The liver protein decreased and bilirubin levels elevated potentially ($P < 0.05$) in toxin-induced animals. After, the treatment with silymarin, leaves and bark extracts, there was a significant improvement in the liver parameters was observed when compared to the control ($P < 0.05$). Table 4 represents the Na^+K^+ ATPase, Mg^{2+} ATPase and Ca^{2+} ATPase levels in the experimental and control groups. The activities of the mentioned enzymes were reduced significantly ($P < 0.05$) in toxin-induced animals. The silymarin and ethanolic leaves and bark extract of the plant treatment significantly normalized the altered levels in comparison with the normal control ($P < 0.05$).

Fig. 1 represents that the histopathological evaluation of rat livers of the experimental and control groups. The liver of (Fig. 1A) rats in the control group was found to be normal with a central vein and

Table 1
Effect on body and liver weight in the experimental groups.

Groups	Bodyweight (g)	Liver weight (g)
G1	160.33 \pm 0.88 ^a	5.86 \pm 0.09 ^a
G2	113.50 \pm 0.76 ^b	3.51 \pm 0.12 ^b
G3	123.00 \pm 0.82 ^c	4.33 \pm 0.02 ^c
G4	138.67 \pm 0.92 ^d	4.88 \pm 0.05 ^d
G5	153.83 \pm 0.79 ^e	5.40 \pm 0.0 ^e
G6	118.17 \pm 0.54 ^{cf}	4.16 \pm 0.04 ^f
G7	130.83 \pm 0.70 ^g	4.41 \pm 0.04 ^c
G8	146.67 \pm 0.88 ^h	5.05 \pm 0.06 ^d
G9	156.67 \pm 1.48 ^e	5.54 \pm 0.06 ^e
G10	156.83 \pm 0.48 ^e	5.73 \pm 0.01 ^{a,e}

Values are expressed in mean \pm SD ($n = 6$).

Mean values in the same column with different superscript from a to h are different P values.

Table 2

Effect on LDH, GGT, lipase and CK of experimental groups.

Groups	LDH (U/L)	GGT (U/L)	Lipase (U/L)	CK (U/L)
G1	167.62 ± 4.30 ^a	10.07 ± 0.43 ^a	56.02 ± 1.19 ^a	169.50 ± 3.13 ^a
G2	319.68 ± 8.16 ^b	19.98 ± 1.23 ^b	89.11 ± 1.92 ^b	909.67 ± 9.17 ^b
G3	280.36 ± 4.82 ^c	15.51 ± 0.26 ^c	80.11 ± 1.35 ^c	704.83 ± 7.90 ^c
G4	224.92 ± 6.31 ^d	13.47 ± 0.16 ^d	69.43 ± 1.17 ^d	531.67 ± 8.86 ^d
G5	170.85 ± 2.98 ^a	11.57 ± 0.38 ^{a,e}	59.33 ± 0.70 ^c	180.17 ± 1.92 ^{a,e}
G6	297.15 ± 7.29 ^e	16.58 ± 0.42 ^c	82.21 ± 0.68 ^c	763.33 ± 6.79 ^f
G7	236.43 ± 5.68 ^d	15.00 ± 0.28 ^c	73.26 ± 1.04 ^d	564.17 ± 19.21 ^d
G8	179.44 ± 2.11 ^f	12.64 ± 0.36 ^{a,e}	62.52 ± 1.95 ^e	205.83 ± 10.19 ^e
G9	168.32 ± 1.68 ^a	11.10 ± 0.31 ^a	57.14 ± 0.98 ^a	174.67 ± 3.92 ^a
G10	167.91 ± 2.20 ^a	10.10 ± 0.52 ^a	56.92 ± 0.91 ^a	168.81 ± 3.19 ^a

Values are expressed in mean ± SD (n = 6).

Mean values in the same column with different superscript from a to f are different P values.

LDH: lactate dehydrogenase; GGT: gamma glutaryl transferase; CK: creatine kinase.

Table 3

Effect on protein, direct bilirubin and total bilirubin of experimental groups.

Groups	Protein (mg/dl)	Direct Bilirubin (mg/dl)	Total Bilirubin (mg/dl)
G1	9.42 ± 0.04 ^a	0.73 ± 0.01 ^a	0.88 ± 0.01 ^a
G2	4.71 ± 0.40 ^b	1.32 ± 0.01 ^b	1.62 ± 0.03 ^b
G3	5.64 ± 0.18 ^c	1.11 ± 0.10 ^c	1.37 ± 0.01 ^c
G4	7.39 ± 0.19 ^d	1.01 ± 0.01 ^d	1.16 ± 0.00 ^d
G5	9.02 ± 0.04 ^a	0.77 ± 0.01 ^a	0.95 ± 0.00 ^a
G6	5.10 ± 0.05 ^c	1.20 ± 0.02 ^e	1.44 ± 0.01 ^e
G7	6.86 ± 0.08 ^b	1.08 ± 0.02 ^d	1.29 ± 0.04 ^{c,d}
G8	8.79 ± 0.11 ^a	0.84 ± 0.02 ^a	1.04 ± 0.03 ^a
G9	9.20 ± 0.03 ^a	0.76 ± 0.00 ^a	0.92 ± 0.00 ^a
G10	9.48 ± 0.05 ^a	0.71 ± 0.01 ^a	0.89 ± 0.01 ^a

Values are expressed in mean ± SD (n = 6).

Mean values in the same column with different superscript from a to f are different P values.

Table 4Effect on Na⁺K⁺ ATPase, Ca²⁺ ATPase and Mg²⁺ATPase of the animals.

Groups	Na ⁺ K ⁺ ATPase (µg of pi liberated/g tissue/min)	Ca ²⁺ ATPase	Mg ²⁺ ATPase
G1	61.2 ± 1.4 ^a	78.04.7 ^a	100.3 ± 0.9 ^a
G2	37.2 ± 1.0 ^b	49.0 ± 0.4 ^b	73.4 ± 0.6 ^b
G3	45.4 ± 0.6 ^c	58.0100.7 ^c	83.0 ± 2.6 ^c
G4	51.8 ± 0.7 ^d	63.6 ± 0.4 ^d	87.4 ± 0.4 ^d
G5	53.2 ± 0.5 ^d	73.0 ± 1.4 ^e	93.4 ± 0.4 ^e
G6	43.1 ± 0.5 ^c	55.2 ± 0.7 ^c	80.2 ± 1.2 ^c
G7	49.0 ± 0.7 ^{d,e}	61.4 ± 0.7 ^d	84.8 ± 0.8 ^f
G8	52.4 ± 0.6 ^d	71.2 ± 0.8 ^e	89.0 ± 0.7 ^d
G9	57.0 ± 0.3 ^f	75.2 ± 0.4 ^f	97.4 ± 0.4 ^g
G10	60.0 ± 0.3 ^{a,f}	76.4 ± 0.5 ^{a,f}	98.4 ± 0.4 ^{a,g}

Values are expressed in mean ± SD (n = 6).

Mean values in the same column with different superscript from a to g are different P values.

Na⁺K⁺ ATPase: sodium-potassium ATPase; Ca²⁺ ATPase: calcium ATPase; Mg²⁺ ATPase: magnesium ATPase.

predominant nucleus. The liver of the rats intoxicated with isoniazid and rifampicin (Fig. 1B) showed hepatocellular alteration, irregular hepatocytes, hydropic degeneration, nuclear congestion, blood spot appearance and vacuolization observed in histoarchitectural examinations, compared with control. The (Fig. 1J) rats treated with *P. pterocarpum* leaves and bark (400 mg/kg) show normal histological architecture respectively. The isoniazid and rifampicin treated (Fig. 1C and Fig. 1D) rats supplemented with *P. pterocarpum* (100, 200 mg/kg) of leaves

showed partial recovery of hepatocytes with mild degeneration.

The isoniazid and rifampicin treated (Fig. 1F and G) rat supplemented with *P. pterocarpum* (100, 200 mg/kg) of barks noted signs of protection and considerable extent as obvious from the formation and regeneration of normal hepatic cells as well as preserved central vein and vacuoles in the histology of the liver. The higher doses of ethanolic extracts of leaves and barks of *P. pterocarpum* (400 mg/bw) treated rats (Fig. 1E and H) rescued the normal morphology of the liver as similar to the control. The standard silymarin-treated rats (Fig. 1I) showed normal liver cells with a well-conserved central vein, cytoplasm and prominent nucleus. The plant extracts of leaves and barks of *P. pterocarpum* alone treated group (Fig. 1J) showed the normal hepatic cell architecture, this may prove the harmless nature of the plant extracts.

4. Discussion

The body and liver weight are important indicators of the toxicity of the drug, because of the morphological changes occurring in the toxic conditions. Several factors influence the weight changes including the animal, gender, sex, toxin and environmental conditions (Gur and Waner, 1993). In the current study, the weight of the body and liver is decreased in the isoniazid and rifampicin-treated groups but the weight was significantly increased in the treatment with the leaves and barks extracts of *P. pterocarpum* and the results were compared to the silymarin treated rats. Tersitore et al. (1987) have revealed that a decrease in body weight is noted in ascitic hepatoma-bearing rats with tumour growth. This is due to a reduction in food consumption and its absorption may contribute to muscle wastage in the tumour (Pain et al., 1984).

From the study of Vijayakumar et al. (2018) suggested that the ethanolic extract of *Psidium guajava* and quercetin fraction from *P. guajava* had a protective effect against the oxidative stress in the HepG2 cell line induced by the carbon tetrachloride (CCl₄). The findings of the current investigation also prove the protective effect of the ethanolic extract of leaves and bark on liver cells. In a dosage-dependent manner, the *P. pterocarpum* leaves have higher activity when compared to the bark extract. The plant extract alone treated group has a similar value when compared with the normal control rats. This proves the protection of the plant without side effects. The LDH is an important enzyme in the glycosylase family; it occurs in the cytoplasm of tissues and is mainly present in the kidney. In the current study, in the toxin-treated rats, the concentration of LDH is highly elevated. Then the treatment of leaves and barks of the extract of the plant reduces the level, which is nearer to the standard drug-treated animals. The GGT is a peptidase, that catalyses the transfer of gamma glutaryl group from peptides. The level of GGT is increased in the hepatic damage condition (Carla et al., 2016). The findings of the current study highlighted that the GGT were elevated in the toxin-induced animals, and the treatment with plant leaves and bark extract the content was restored. This may prove the recovery of the hepatic damage. The CK is a cytosolic enzyme. It is the most sensitive enzyme to muscle damage. The administration of leaves and bark of plant extract may reduce CK. The lipase enzyme helps to digest fats present in the diet up to 50–70% and also increases the risks of vitamin deficiencies and liver diseases. The findings of the current study presented that the toxin-treated rats showed an increase in lipase. After the treatment of leaves and bark extracts, the level of lipase is considerably decreased. A similar effect is noted in the earlier study of Maqsood et al. (2017).

The liver regulates the synthesis of protein. Hepatic damage due to the toxins such as isoniazid and rifampicin alters the synthesis and metabolism of liver glycogen and protein (Andrea and Harugara, 1987). The levels of protein and glycogen were stimulated by the administration of ethanolic leaves and bark extract of the plant. This may be due to the hepatoprotective property of the leaves and bark extract. In this study, the extract prevents the deamination process and retains the protein level, as well as some enzymes, that regulate the glucose conversion into glycogen. The previous study of the treatment of *Tricholepis*

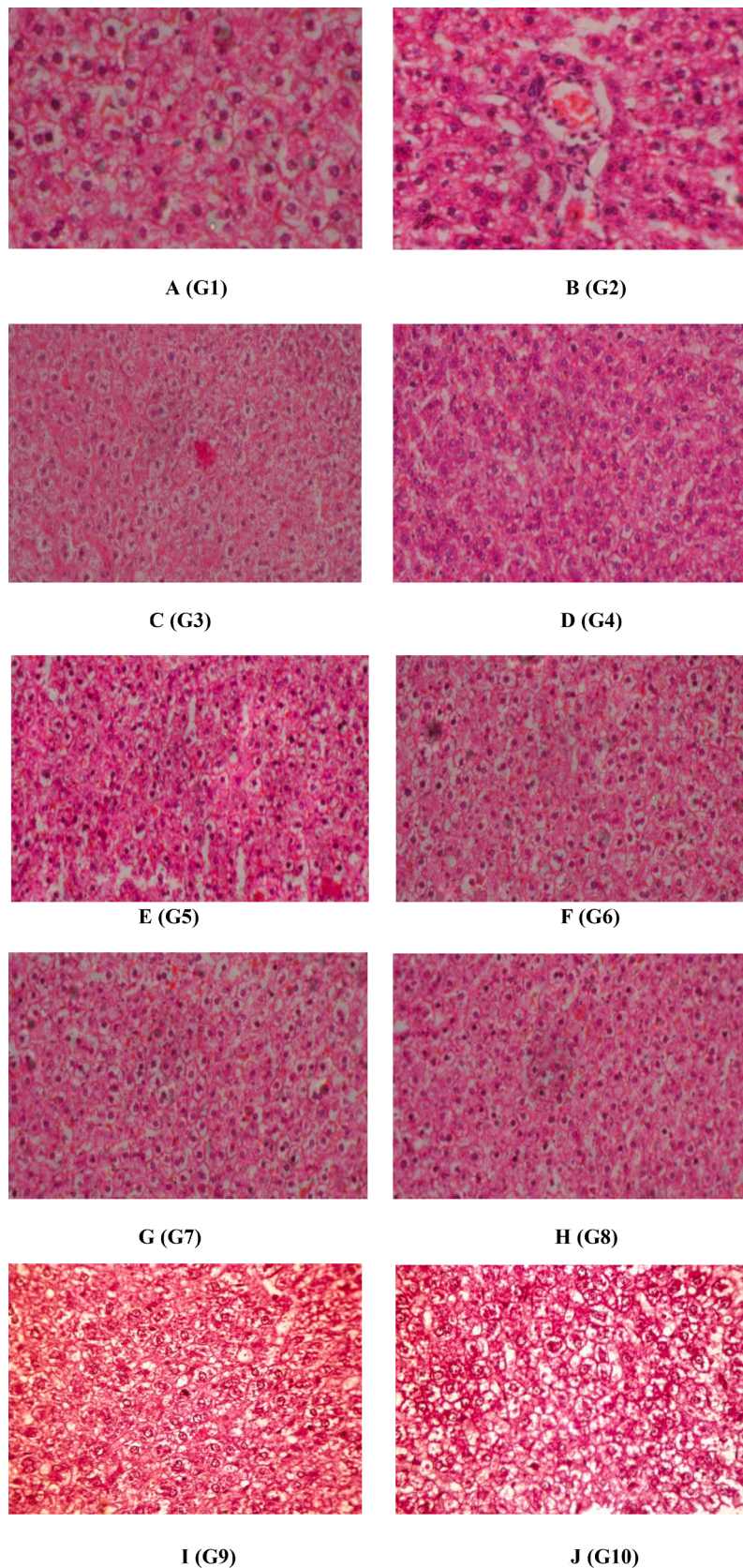


Fig. 1. (A to J/G1 to G 10). The histopathological examination of liver of the control and experimental rats. 1A) Control (basal diet and saline water, G1-group 1), 1B) untreated- Isoniazid and rifampicin induced as negative control (G2), 1C) G2 administered with 100 mg/kg of leaf extract of *P. pterocarpum* (G3), 1D) G2 administered with 200 mg/kg of leaf extract of *P. pterocarpum* (G4), 1E) G2 administered with 400 mg/kg of leaf extract of *P. pterocarpum* (G5), 1F) G2 administered with 100 mg/kg of bark extract of *P. pterocarpum* (G6), 1G) G2 administered with 200 mg/kg of bark extract of *P. pterocarpum* (G7), 1H) G2 administered with 400 mg/kg of bark extract of *P. pterocarpum* (G8), 1I) 25 mg/kg of silymarin (G9) and 1 J) G2 administered with both leaf and bark extract (G10).

radicans in toxin-induced hepatic rats increases the protein and glycogen levels. John et al. (2011). *Gracilaria corticata* alters the liver enzymes in AFB1-induced hepatotoxicity (Manoharan et al., 2008). This may be proven by the present study also.

According to the study of Friedman et al. (1978) stated that bilirubin is the end product of haemoglobin; it binds to albumin and migrates to the liver, where it is bound to glucuronic acid and excreted in bile. The rise in bilirubin concentration is directly proportional to hepatic dysfunction due to the toxin. In the current study, the level of bilirubin is elevated because of the toxicity induced by isoniazid and rifampicin. In this investigation, after the administration of leaves and bark extract of the plant, the level of direct and total bilirubin was decreased. Hepatotoxins can decrease the protective effect of the hepatoprotective drug that can preserve the normal activity of the liver. The ATPase is mainly involved in the translocation process of sodium, potassium, calcium and magnesium. The enzyme ATPase regulates the electrolytes in cells and cellular membranes. In liver toxic conditions, alterations occur in the structure of the membrane and it reduces the enzyme level in the blood (Premalatha and Sachidanandam, 1998). Ionic homeostasis and the physiological function of the liver are dependent on trans membranous enzymes like Ca^{2+} ATPase and $\text{Na} + \text{K} + \text{ATPase}$ (Frolkis et al., 1999). The study of Chandramohan et al. (1996), who stated that the enzyme Na^+K^+ ATPase regulates the intracellular Na^+ concentration and water content in the cell. The Na^+K^+ ATPase inhibition has been reported as a key regulator to minimize cellular metabolism. Ca^{2+} ATPase is mainly involved in the regulation of Ca^{2+} pumping action and it is also involved in the contraction of the muscles and also the neurosecretion process. The decreasing concentration of the levels of protein is associated with the decreasing level of Ca^{2+} ATPase (Hemmings et al., 2002). In the current study, the protein content is reduced and it may reduce the Ca^{2+} ATPase level. Mg^{2+} ATPase is pivotal in the electrolyte transport across the biological membrane. In toxic conditions, the membrane permeability is disturbed and this may be due to the lower concentrations of Mg^{2+} ATPase. Overall, the protective nature of the plant extract may prevent the cellular membrane from toxin-induced damage and it restored the level of membrane-bound enzymes. In the current investigation, the histopathology changes also support the hepatoprotective efficacy of *P. pterocarpum* in the toxin-induced animal model. The changes seen are supportive of the studies by Adedapo et al. (2005) who have described the plant extracts of *Phyllanthus amarus* restored the liver histology against toxin-induced hepatotoxicity. This also explains the restoration of enzymes shown by the groups in the current investigation.

5. Conclusion

The findings of this investigation suggest the protective effect of the *P. pterocarpum* leaves and bark extract on the liver markers and membrane-bound enzymes against the toxin-treated rats. This result demonstrates that *P. pterocarpum* leaves and barks are hepatoprotective. However, further identification of effective bioactive compounds from the extract needs to be done. The limitation of the present investigation is the lack of molecular studies which may provide the mechanism of action of the lead compound at the cellular level.

CRedit authorship contribution statement

Maria Jerline Babu: Writing – original draft, Methodology, Formal analysis, Data curation. **Ramasamy Manikandan:** Writing – original draft, Resources, Methodology, Formal analysis. **Balasubramanian Balamuralikrishnan:** Writing – review & editing, Writing – original draft, Resources, Investigation. **Bharathi Kathirvel:** Resources, Methodology, Formal analysis. **Rajakrishnan Rajagopal:** Writing – review & editing, Visualization, Validation. **Ahmed Alfarhan:** Writing – review & editing, Visualization, Validation, Resources. **Arun Meyyazhagan:** Writing – review & editing, Visualization, Resources, Formal analysis. **Arumugam Vijaya Anand:** Writing – review & editing, Validation,

Supervision, Resources, Project administration, Funding acquisition.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Institutional review board statement

The experimental protocols and handling of animals were authorized by the Institutional Animal Ethics Committee, Srimad Andavan College of Arts and Science, Tiruchirappalli, Tamil Nadu, India (Approval No.: SAC/IAEC/BC/2016-/Ph.D.-007).

Data availability statement

The authors confirm that the data findings that support this study are available upon request with corresponding author.

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