RESEARCH PAPER

Hepatoprotective Effects of Leaves of Dysoxylum Malabaricum an Endangered Medicinal Plant and Its Isolated Compound against Paracetamol Induced Hepatotoxicity in Rats

Sangeetha PT[1], Venkatachalam T[2*] and Kalaiselvi P[2]

[1]Mohamed Sathak A.J.College of Pharmacy, Medavakkam High Road, Sholinganallur, Chennai, Tamil Nadu, India
[2]JKKMMRFs Annai JKK Sampoorani Ammal College of Pharmacy, Komarapalyam, Namakkal, The Tamil Nadu Dr. MGR Medical University, Tamil Nadu, India*

Received: 15th Sep, 2025; Revised: 15th Oct 2025; Accepted: 16th Nov, 2025; Available Online: 1st December, 2025

ABSTRACT

The present study examines the hepatoprotective effects of the leaf extract (DME) of Dysoxylum malabaricum (Indian white cedar) and an isolated compound (IDM) of this plant on hepatoprotection against paracetamol-induced liver toxicity in albino Wistar rats. The acute oral toxicity was tested using ethanol-extracted leaf fractions which were separated using column chromatography. After the hepatotoxicity caused by paracetamol, rats were grouped and subjected to DME, IDM or hepatoprotective agent silymarin. Biochemical indicators, such as ALT, AST, ALP, bilirubin, and antioxidant enzymes (SOD, CAT, GPx), and histopathological examinations of liver tissue were used as protective measures. The results showed that at higher doses (500mg/kg DME and 50mg/kg IDM), both of the treatments enhanced the liver functioning markers, reconstituted the antioxidant levels of the enzymes, and lowered lipid peroxidation. It is worth noting that IDM exhibited a strong tissue regeneration and dose-effect in the histopathological analysis. Their protective effects were also enhanced by the improvement of lipid profiles and body weight. On the whole, the research confirms that D. malabaricum and IDM have important hepatoprotective potential, which proves their traditional application in ethnomedicine and promotes their future pharmaceutical exploitation as agents against liver diseases. These findings are supportive to the ongoing clinical studies, which would legitimize and apply these findings into therapeutic use.

Keywords: Dysoxylum malabaricum, hepatoprotection, paracetamol-induced hepatotoxicity, antioxidant enzymes, liver function markers, lipid profile, histopathology.

How to cite this article: Sangeetha PT, Venkatachalam T, Kalaiselvi P, Hepatoprotective Effects of Leaves of Dysoxylum Malabaricum an Endangered Medicinal Plant and Its Isolated Compound against Paracetamol Induced Hepatotoxicity in Rats. Int J Drug Deliv Technol. 2026;16(1): 649-658. DOI: 10.25258/ijddt.16.1.67

Source of support: Nil.

Conflict of interest: None

INTRODUCTION

The liver supports the systemic homeostasis process by managing detoxification, intermediary metabolism, and the synthesis of vital plasma proteins[1]. Hepatotoxicity refers to damage caused by a potentially hazardous exposure, most often drugs, chemicals, or pollutants, and it includes various clinical and histopathological liver diseases[2]. Drug-induced liver injury (DILI) is one of the most common causes of liver morbidity in the world. The most commonly used classes such as NSAIDs, antibiotics and anti-retrovirals are implicated repeatedly[3]. It is known that acetaminophen (paracetamol) produces reactive intermediates in the liver that cause severe oxidative stress, sterile inflammation, and liver cell death when consumed in overdose[4,5]. As the global consumption continues to increase, there is an urgent need to have effective and liver-targeted interventions.

Part of the purpose of standard care is to prevent the progression and alleviate complications. Paracetamol toxicity uses n-acetylcysteine (NAC) as the antidote of choice and corticosteroid or other immunosuppressants are left as a last resort in autoimmune causes[6,7]. However, such

**Author for Correspondence:* venkatachalammpharm@yahoo.co.in

approaches may have negative side effects and in many cases do not achieve full recovery of lost hepatic structure and function after injury has occurred. In turn, plant-based hepatoprotectants with combined antioxidant and anti-inflammatory effects are of great interest, which is often attributed to flavonoids, limonoids, and triterpenoids[8,9].

The ethnomedicinally important plant, *Dysoxylum malabaricum* (Indian white cedar) belonging to family, Meliaceae has also been emerging as an important source of terpenoids in liver protection. Its fruits were recently phytochemically studied and found to contain six triterpenoid compounds, all previously undocumented in the species, together with in-vitro cytotoxic testing and in-silico work with molecular-dynamics support[10]. The research works on previous leaf and bark lead to isolation of apotirucallane/tirucallane and cycloartane triterpenoids, and even a unique ergostane derivative[11,12]. Members of meliaceae have long been reported to combat reactive oxygen species, regulate NF-kappa B and other inflammatory pathways, and support cell membranes, all of which are consistent with the pathobiology of DILI[13,14]. It is worth mentioning that *D. malabaricum* extracts and purified triterpenes have demonstrated sound bioactivity in other models of stress and inflammation (e.g., potent and dose-dependent activity against Anopheles stephensi life stages), highlighting membrane-active and redox-pertinent pharmacology[15].

Collectively, the chemical pedigree (limonoids, tirucallanes, cycloartanes, ergostanes) and bioactivity signal offers an overriding hypothesis that *D. malabaricum* may mitigate the oxidative radicals and downstream inflammatory harm caused by paracetamol, thus alleviating serum transaminases, antioxidant enzyme status and histopathology in vivo. We hypothesized that the plant extract might alleviate oxidative and nitrosative stress, normalize hepatic activity and revert hepatic microarchitecture. The results are studied by the modification of biochemical markers (e.g., ALT, AST, ALP, bilirubin), antioxidant defenses (GSH, SOD, CAT, MDA), and histopathology compared to toxic and standard control drugs. Favorable results would support the ethnomedicinal claims of *D. malabaricum* and encourage isolation-driven investigations that could identify lead molecules in the future pharmaceutical development.

METHODOLOGY

Collection and extraction process

The leaves (1 kg) of *Dysoxylum malabaricum* were bought in January, in a local herbal market in Chennai, India. The plant was dried for 7 days under shade after washing thoroughly to remove dust and debris. The material was then sieved through a #40 mesh after being ground to a fine powder when completely dry. Extraction of the powder was performed with ethanol in a Soxhlet apparatus. The resulting extract (DME-22.58% w/w) was filtered, concentrated with the help of a rotary evaporator and keep in air-tight container at 4ºC until further use[16,17].

Fraction isolation

The predetermined quantity of n-hexane mixed with a mixture of 2 gm thick ethanol extract and silica gel medium (100- 200 mesh size) was thoroughly mixed in mortar. A trituration step and a solvent evaporate were done in order to guarantee that their mixture was freely flowing. After loading the column with the sample, n-hexane was introduced into the column and left overnight so as to allow it to settle so as not to disorient the mixed extract. The column was run through a gradient elution with a series of organic solvents in order of increasing polarity of each solvent. The mixture of Ethyl acetate and Hexane was used to elute the extract in different proportions (10:90, 20:80, 30:70, 40:60, 50:50, 60:40, 70:30, 80:20, 90:10 and finally ethyl acetate 100%) and fractions (200mL each) obtained at the column was collected and combined under TLC monitoring.

Maintenance of animals

The healthy young adult albino Wistar rats used in the study included both sexes. The animals used were between 6 to 8 weeks old at the beginning of dosing, weighed 150-200 grams and did not differ by more than 20% of the average weight of animals previously dosed. The ambient temperature of the experimental animals was set at 22±3ºCelsius and the relative humidity was maintained at 30%. Lighting was provided

artificially for 12 hrs of light and dark cycles. The lab-standard diets were supplied to the animals regularly and drinking water was available without any limitation. The dose determined their placement in group cages in a way that the animals per cage did not interfere with the clear observation of each animal.

Acute Oral Toxicity Studies

The experiment was carried out according to OECD 423 (Acute Toxic Class Method) that is executed in phases and in each phase, three of the same sex animals are used. The study used adult Wistar rats of 180-200g. The extract and isolated compound were dosed orally at 2000 and 500 mg/kg body weight since most of the compounds usually possess LD50 greater than 200 and 50 mg/kg, respectively. Rats were starved overnight and allowed free access to water and the dose was administered by mouth. Post administration, the animals were deprived of food between 3-4 hours and they were closely observed to ensure no toxicity was exhibited.

Paracetamol Induced Hepatoxicity

Hepatoprotective activity is a standard test which is conducted to establish the possibility of a substance protecting the liver under the influence of multiple agents. In general, the process of examining the hepatoprotective effect of DME and isolated fraction IDM on paracetamol-induced hepatotoxicity in albino Wistar rats was in comparison to Somnambularin[18].

Grouping

The albino Wistar rats will generally be categorized into 7 groups:

Group I: Control group - Orally received normal saline (1 mL/kg) in 28 days.

Group II: Induced group - The group was administered a 3g/kg bw dose of Paracetamol orally in 14 days.

Group III: Silymarin - Paracetamol at a dose of 3 g/kg bw along with silymarin at a dosage of 50 mg/kg/day in the form of oral dosage.

Group IV: Extract of Dosyxylum malabaricum (DME): - DME was administered orally as 200mg/kg/day along with paracetamol at a dose of 3 g/kg bw.

Group V: Extract of Dosyxylum malabaricum (DME)- DME was orally administered at the dose of 500 mg/kg/day along with the paracetamol dose of 3 g/kg bw.

Group VI: Isolated fraction of Dosyxylum malabaricum (IDM)- IDM was administered orally to the group of 25mg/kg/day together with paracetamol at a concentration of 3 g/kg bw.

Group VII: Isolated fraction of Dosyxylum malabaricum (IDM)- A personage IDM orally at a dose rate of 50mg/kg/day combined with paracetamol at a dose rate of 3g/kg bw.

Blood collection and processing

After completion of experimental regimen (28^{th} day), animals were kept overnight fasting and anaesthetized with thiopentone sodium (40mg/kg/i.p), blood samples for haematological and biochemical analysis were collected into separate tubes with and without EDTA-K_2. The tube which had 0.3 mL of blood with anticoagulant used for haematological analysis and the other tubes were used for separation of plasma / serum which was used for various biochemical parameters. After completion of the blood collection, animals were euthanized withexposure to CO_2. Necropsy of Liver was observed and histopathological changes was noted. A known weight of liver was used for homogenate preparation and used for various biochemical analyses[19-21].

The vial containing EDTA-K_2 tubes were used for separation of plasma by centrifugation in high speed cooling centrifuge (Remi C-24) at 4°C for 10 minutes at 3000 rpm. After clotting the blood, tubes were centrifuged 3000rpm for 10 minutes to separate the serum. Plasma/Serum biochemical parameters (Liver function parameters, kidney function parameters, Protein profile, lipid profile) were estimated by Clinical chemistry fully auto analyser (XL-640) using kits from ERBA.

Preparation of liver tissue homogenate

To obtain the supernatant to carry out the lipid peroxidation (TBARS) test, the isolated liver was homogenized in phosphate buffer (0.01M, pH 7.0) to obtain a ten percent (w/v) homogeneous. Another centrifugation of the aliquot at 12,000u g/20 minutes at 4 o C was carried out to get the post mitochondrial supernatant (PMS). The

transparent supernatant was immediately estimated regarding lipid peroxidation markers and other enzyme and non-enzyme antioxidant substances. The parameters were MDA, SOD, CAT, GPx, GST, GR, glutathione, vitamin C and E which were evaluated using the normal methods[22-24].

Histopathological studies

The similar procedure for slicing, fixation and staining to study the histology of the liver tissue was performed according to standard procedure was applied and liver tissue was studied.

Statistics

Values were given as mean±SEM. The statistical analysis was conducted by using one-way analysis of variance (ANOVA) followed by the implementation of a Tukey -Kramer post hoc test to conduct multiple comparisons in groups. The software used to carry out all the analyses is Graphpad Prism 5, and a p -value of less than 0.05 was taken as significant.

RESULTS

The column chromatography yielded 4 fractions coded as fraction 1 (12.61%w/w), fraction 2 (14.77%w/w), fraction 3 (22.47% w/w) and fraction 4 (8.04% w/w). The fraction with highest yield was selected and further subjected to TLC using n-hexane: ethyl acetate:acetone (60:30:10) as mobile phase which showed only one spot, confirming the presence of only 1 compound in the fraction. Hence this fraction was considered as isolated compound (IDM) and recrystallized using ethanol.

Acute oral toxicity studies

The effects of DME (2000 mg/kg) and IDM (500 mg/kg) on the body weight, feed intake and the water intake of rats over 14 days during acute toxicity tests were presented in this table. Body weight of rats in Control group recorded a gradual rise between day 1 and day 14. Relatively steady body weight development was obtained in both DME and IDM groups, implying that the doses used did not have major adverse impacts on overall growth.

Table 1: Effect of DME and IDM on the body weight in Acute Toxicity Studies

Parameter	Groups	Day 1	Day 7	Day 14
Body weight (g)	Control	181.45±0.29	191.77±1.08	192.62±2.07
	DME2000	182.46±2.28	188.08±1.38	192.48±0.76
	IDM500	181.32±2.16	188.15±2.62	192.56±1.87
Feed intake (g)	Control	12.71±0.18	13.93±0.59	14.32±1.23
	DME2000	13.08±0.24	14.18±0.68	13.88±0.71
	IDM500	13.24±1.11	14.31±1.46	14.44±1.54
Water intake (ml)	Control	21.45±0.86	23.52±0.98	26.07±0.21
	DME2000	21.73±0.61	24.39±0.62	26.62±1.60
	IDM500	21.39±0.87	23.41±1.87	25.61±1.82

Effect of DME on Body Weight in Paracetamol-Induced Hepatotoxicity

Table 2 shows the influence of CAE on the body weight alteration in a paracetamol model of hepatotoxicity during 28 days. In the Control group, the body weight consistently increased during the study period as the body weight measured on Day 1 (211.83g) rose to 245.16g on Day 28. Comparatively, the Induced group that was administered with paracetamol to promote hepatotoxicity showed a significant drop in weight to the extent of 212.16g on Day 1 to 173.5g by Day 28, which was interpreted as the harmful effects of the induced agent. The standard drug group demonstrated a significant body weight recovery. There was more pronounced improvement in the DME500 group with maximum achieved score of 249.89 g on Day 28, which was statistically significant ($p < 0.001$). Recovery was also observed in the IDM25 and IDM50 groups and the IDM50 group had a significant rise in body weight to 247.36 g on Day 28 indicating dose-dependent effect. The results show that both DME and IDM can offer protective effects against paracetamol-induced hepatotoxicity, which restores a normal body weight, thus demonstrating their possible hepatoprotective effects.

Table 2: Effect of DME on the changes in body weight in Paracetamol induced hepatotoxicity

Groups	Initial	day 14	day 28
Control	211.83±3.54	226.66±3.32	245.16±2.13
Induced	212.16±2.48	193.83±3.18	173.5±2.50
Standard	213.16±1.83	242.16±1.72***	253.33±2.33***
DME250	212.08±2.42	208.55±2.60	222.34±2.65**
DME500	212.45±2.35	230.76±2.45**	249.89±2.27***
IDM25	212.00±2.40	213.82±2.86*	227.66±2.90**
IDM50	212.23±2.38	228.24±2.50**	247.36±2.45***

The values were represented as mean±SEM; the values were considered significant at *P<0.05; **P<0.01 and ***P<0.001 compared to induced group

Effect of DME and Isolated Compound on Lipid Parameters in Paracetamol-Induced Hepatotoxicity

The table 3 displays the influence of DME and IDM on the parameters of the lipid profile including total cholesterol (TC), triglycerides (TG), high-density lipoprotein (HDL), low-density lipoprotein (LDL), and very-low-density lipoprotein (VLDL) in paracetamol-induced hepatotoxic animals. The control group had a normal level of lipids compared to the induced group which recorded a significant elevation in total cholesterol (199.46 mg/dL), triglycerides (173 mg/dL), VLDL (34.89 mg/dL) and a reduction in HDL (23.73 mg/dL) and a drastic increase in LDL and VLDL. The lipid metabolism in the IDM treated groups exhibited desirable results in both IDM25 and IDM50. IDM50 showed the maximum improvement in lipid parameters, with TC (83.26 mg/dL), TG (79.22 mg/dL), HDL (36.18 mg/dL), LDL (34.69 mg/dL) and VLDL (15.87 mg/dL) shifting to normal. DME and IDM in high doses suggested that there was significant improvement in lipid profiles over the induced group. The results indicate that DME and IDM may hold promise of providing a beneficial change in lipid metabolism and eliminating the adverse effect of paracetamol-induced hepatotoxicity.

Table 3: Effect of DME and IDM on Lipid Parameters in Paracetamol induced hepatotoxicity

Groups	TC (mg/dL)	TG (mg/dL)	HDL (mg/dL)	LDL (mg/dL)	VLDL (mg/dL)
Control	80.14±2.78	71.69±2.20	31.45±2.32	34.62±2.48	14.71±1.30
Induced	199.46±5.46	173.00±3.55	23.73±1.35	140.98±4.66	34.89±1.33
Standard	89.67±3.41***	88.32±3.05***	37.09±2.63***	34.81±2.74***	17.80±0.91***
DME250	132.88 ± 4.90*	128.75 ± 4.87*	26.17 ± 1.61*	91.15 ± 3.77**	27.38 ± 1.20**
DME 500	90.12 ± 3.18***	90.44 ± 2.89**	33.98 ± 2.26***	36.48 ± 2.38***	18.25 ± 0.88***
IDM25	115.45 ± 4.23**	112.56 ± 4.32*	28.84 ± 1.78**	78.36 ± 3.42***	23.44 ± 1.12***
IDM50	84.79 ± 2.92***	76.88 ± 2.47***	35.62 ± 2.40***	35.02 ± 2.25***	16.12 ± 0.95***

*The values were represented as mean±SEM; the values were considered significant at *P<0.05; **P<0.01 and ***P<0.001 compared to induced group*

Effect of DME and Isolated Compound on Hepatic Parameters in Paracetamol-Induced Hepatotoxicity

Table 4 demonstrates the effect of DME and IDM treatment on the hepatic markers in a paracetamol-induced hepatotoxicity. The Induced group exhibited the severe damage of the liver, the levels of ALT, AST, ALP, LDH and bilirubin were also increased; the level of total protein (TP) was also decreased. The Standard group, on the other hand, treated with a hepatoprotective agent indicated a significant recovery of all markers with a similarity to controls. Both DME250 and DME500 treatments led to partial improvements, with DME500 to more pronounced recovery. Both the IDM25 and IDM50 groups demonstrated dose-dependent protective effect, with the latter group of IDM50 approaching normal values in the majority of hepatic parameters.

Table 4: Effect of DME and IDM on Hepatic Markers in Paracetamol induced hepatotoxicity

Groups	TP (mg/dL)	ALT (U/L)	AST (U/L)	ALP (U/L)	LDH (U/L)	Bilirubin (mg/dL)
Control	8.76±0.33	27.51±1.80	46.05±2.40	122.61±4.47	123.21±5.72	0.945±0.18
Induced	4.77±0.26	56.77±2.07	94.69±2.62	248.32±4.07	246.37±5.78	3.180±0.42
Standard	8.41±0.68***	29.73±1.20***	49.55±1.50***	145.75±3.10***	145.72±2.91***	0.920±0.10***
DME 250	5.83 ± 0.38*	46.88 ± 1.91*	76.29 ± 2.18**	201.37 ± 3.94*	200.51 ± 4.27*	2.36 ± 0.28*
DME500	8.12 ± 0.36***	30.41 ± 1.33***	50.83 ± 1.63***	148.91 ± 3.21***	148.83 ± 3.20***	0.99 ± 0.12***
IDM 25	6.79 ± 0.40**	42.63 ± 1.85*	70.42 ± 2.10**	188.64 ± 3.85**	189.26 ± 4.10**	2.12 ± 0.26*
IDM 50	8.26 ± 0.35***	28.32 ± 1.25***	48.18 ± 1.57***	139.22 ± 3.00***	138.61 ± 3.10***	0.92 ± 0.11***

The values were represented as mean±SEM; the values were considered significant at *P<0.05; **P<0.01 and ***P<0.001 compared to induced group

Effect of DME on Anti-oxidant parameters in Paracetamol-Induced Hepatotoxicity

Table 5 shows the effects of DME and IDM on different antioxidant markers of rats with hepatotoxicity induced by paracetamol. Such markers are superoxide dismutase (SOD), catalase (CAT), glutathione peroxidase (GPx), glutathione reductase (GR) and lipid peroxidation (LPO) that are important in evaluation of oxidative stress response of the liver. Treatment of the Induced group with paracetamol led to a large decrease in the levels of all antioxidant markers with SOD (3.581 U/mg), CAT (5.561 U/mg), GPx (7.228 umol/mg protein/min), and GR (32.36 mol/mg protein/min) being reduced significantly. The high LPOs values (33.20 nM/mg protein) indicate greater lipid oxidative protection in the liver indicating the characteristic feature of paracetamol toxicity. The mean changes in all antioxidant markers were significantly improved in the Standard group. The hepatoprotective action of the treatment was reflected in SOD (6.128 U/mg), CAT (9.54 U/mg), GPx (16.26 umol/mg protein/min), and GR (53.23 umol/mg protein/min), which were significantly elevated, and LPO (18.69 nM/mg The DME500 group displayed a substantial improvement in all of the markers, with CAT (9.68 U/mg), CAT (9.68 U/mg), SOD (6.21 U/mg), and GPx (16.73 0.88 U/mg protein/min) similar to those of the standard group. The IDM50 group showed the greatest activity, with SOD (6.35 2 0.46 U/mg), CAT (10.05 2 0.55 U/mg), and GPx (17.45 umol/mg protein/min) having reached those of Standard group. Also significantly increased was GR (54.13 umol/mg protein/min) and LPO (19.13 nM/mg protein) returned to near control levels ($p < 0.001$). Both DME and IDM were antioxidant and with higher doses showed more improvement in the markers of oxidative stress. These results indicate that DME and IDM have protective action towards paracetamol induced liver oxidative damage

Table 5: Effect of DME and IDM on Antioxidant Markers in Paracetamol induced hepatotoxicity

Groups	SOD (U/mg)	CAT (U/mg)	GPx (µmol/mg protein/min)	GR (µmol/mg protein/min)	LPO (nM/mg protein)

Control	7.643±0.65	11.11±1.16	19.13±1.26	55.35±2.48	19.25±1.47
Induced	3.581±0.34	5.561±0.59	7.228±0.56	32.36±2.50	33.20±2.88
Standard	6.128±0.51***	9.54±0.48***	16.26±1.00***	53.23±2.11***	18.69±0.33***
DME 250	4.43 ± 0.40**	6.85 ± 0.60*	10.52 ± 0.71**	39.62 ± 2.42*	27.14 ± 1.97**
DME 500	6.21 ± 0.48***	9.68 ± 0.52***	16.73 ± 0.88***	52.85 ± 2.15***	18.94 ± 1.21***
IDM 25	4.98 ± 0.42**	7.21 ± 0.62**	11.96 ± 0.74***	42.77 ± 2.30 ***	25.73 ± 1.82**
IDM 50	6.35 ± 0.46***	10.05 ± 0.55***	17.45 ± 0.92***	54.13 ± 2.10***	19.13 ± 1.12***

*The values were represented as mean±SEM; the values were considered significant at *P<0.05; **P<0.01 and ***P<0.001 compared to induced group*

Histopathological Findings

These histopathological results as seen in figure 1 were in consonance with the biochemical results. Major damage of the liver tissues was evident in the induced group with hepatocyte necrosis, fatty degeneration and inflammation. Conversely, the liver sections of DME500 or IDM50 treatment groups healed moderately, and there was less hepatocellular damage, and hepatocyte repopulation. In particular, the most impressive tissue repair was shown by the IDM50 group, where the liver tissue had almost normal histological characteristics, with a slight inflammation of inflammatory cells and a normal structure of hepatocytes.

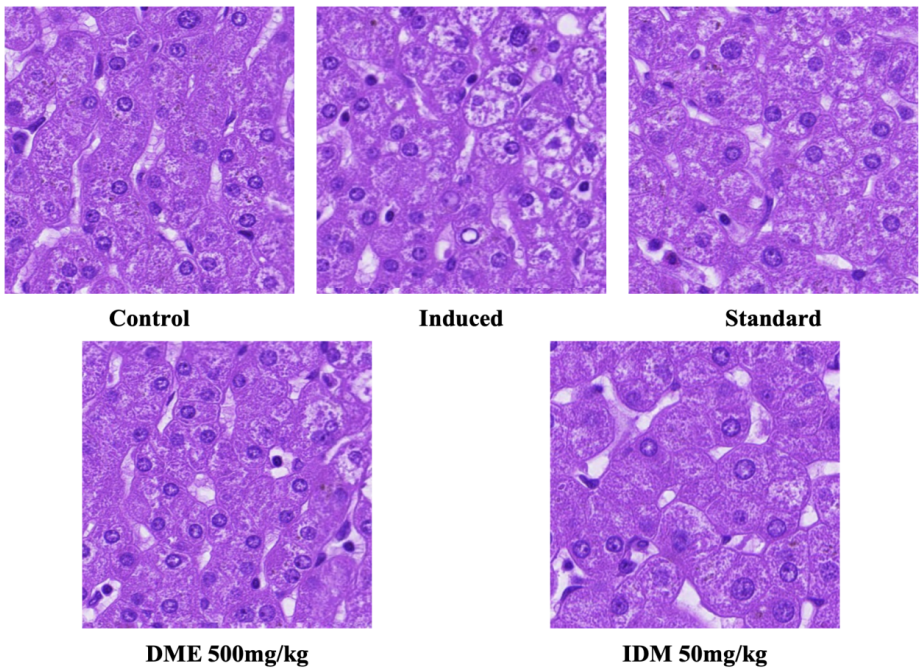

Figure 1: Histopathological Sections of Various Groups in Paracetamol Induced Hepatotoxicity

DISCUSSION

The hepatoprotective mechanism of the DME and IDM was well showcased in the paracetamol induced hepatotoxicity model. Findings of this current research indicated that DME and IDM enhanced body weight significantly in the paracetamol-induced hepatotoxicity model, which signified their role in protecting liver damage.

Plant extracts have previously been reported to possess the ability to protect health against heptotoxic damage, as well as an effective weight reduction effect. According to previous study, the liver functions are primarily focused on metabolic and storage functions, it is believed that DME and

IDM groups gain more weight with the increased metabolic and storage functions. As a result, it seems that regeneration of the liver as well as minimization of liver damage are the most important factors in regaining lost weight once it has been lost[25,26].

In comparison with the induced group, DME and IDM experienced significant variations in their lipid profiles, including a decrease in total cholesterol (TC) triglycerides (TG), LDL and VLDL, and an increase in HDL when compared with the induced group. It has been observed that herbal extracts have similarly modified the lipid profile. The isolated herbal compounds have been shown to lower the level of serum cholesterol and triglycerides, which is consistent with the capability of redressing the lipid metabolism that is often overlooked due to liver damage[27].

It has been shown that the lipid parameters were enhanced after the application of DME and IDM, which indicates that these two techniques are beneficial to fat metabolism. It has also been suggested that DME and IDM may contribute to hepatoprotection through their effects on the metabolism of fats, in addition to controlling liver enzymes involved in lipid synthesis and disintegration[28].

It was observed that IDM had hepatoprotective effects at doses of 25 mg/kg and 50 mg/kg, demonstrating significant changes in liver functioning indexes, such as the levels of alanine aminotransferase (ALT), aspartate aminotransferase (AST), and total protein. Furthermore, DME 250 mg/kg and 500 mg/kg had hepatoprotective effects, with the latter reducing hepatic injury indices more strongly than the former. Many preclinical studies have shown that plant extracts and individual phytochemicals have hepatoprotective effects. Furthermore, silymarin, a hepatoprotectant agent extracted from Silybum marianum, showed similar protection against damage to the liver. Silymarin has been found to restore hepatic enzyme activity (ALT and AST) and improve antioxidant protection during paracetamol-induced oxidative stress[29]. A major cause of hepatic injury was oxidative stress, and DME and IDM have the ability to protect the liver from oxidative damage as a result of the increased activity of the enzymes superoxide dismutase (SOD), catalase (CAT), and glutathione peroxidase (GPx). Hepatocellular damage may be scavenged by these enzymes, which play a critical role in the reduction of reactive oxygen species and the alleviation of the damage in the liver. The IDM compound inhibited the activity of both the glutathione reductase (GR) and lipid peroxidation (LPO) enzymes to a greater extent than adenosine diphosphate (ATP), indicating that it might be able to affect the pathways of producing reduced glutathione (GSH), one of the key antioxidants in hepatocytes. IDM has been reported to have a strong antioxidant capability that has the potential to reduce oxidative stress, especially in cases of dysregulated lipid metabolism, due to its antioxidant properties. An outline the mechanism of how IDM can reduce oxidative stress in hepatic conditions[30].

There was no significant difference between DME and IDM when it came to hepatoprotective activity in the current study, which supports alternative therapies using plant-derived compounds as new therapeutic options in the case of hepatic injury or injury to the liver. While there have been some promising results from the early clinical trials, the next logical step would be to carry these results over to the clinical front so that the clinical trials can verify the preclinical findings. In order to evaluate the pharmacokinetic properties, bioavailability, and safety of these interventions in human subjects, more research needs to be conducted to assess their use. As long as these new hepatoprotective therapeutics prove to be as effective as traditional therapeutics, particularly when it comes to treating chronic liver disease and hepatic injury caused by drugs, they can be considered a viable alternative to the existing hepatoprotective therapeutics. There may be a need for further research to investigate the mechanistic basis of DME and IDM, such as the regulation of hepatic signaling pathways implicated in inflammation and oxidative stress (e.g., NF-kappaB, Nrf2, MAPK). Furthermore, if there are formulation plans aimed at increasing the bioavailability of IDM and DME, then their therapeutic potential can also be increased[31-35]. It is also imperative that clinical trials are performed in order to determine the effectiveness and safety of DME and IDM with regards to their hepatoprotective or anti-inflammatory effects on patients with chronic liver diseases or those taking hepatotoxic drugs in order to determine their impact on these conditions.

CONCLUSION

The study showed a strong evidence that the *Dysoxylum malabaricum* containing its bioactive isolated compound (IDM) possesses a potent hepatoprotective effect against paracetamol-induced acute liver toxicity. In addition to the normalization of major hepatic markers, the extract and isolated fraction (IDM) revealed an excellent improvement in oxidative stress, lipid imbalance, and histopathology damage, which are characteristic features of hepatic damage. The fact that IDM has the potential to match and in some cases even surpass the activity of standard hepatoprotective agent such as silymarin makes it

an object of hope to become a new drug in future medicine. The results do not only confirm the folkloric ethnomedicinal effects on *D. malabaricum*, but also provide a platform to explore more of its molecular action and clinical potential. With the world facing a growing rate of drug-related liver damage, this study sheds a light on the way forward to new, plant-based forms of treatment that may revolutionize the management of liver health.

Conflict of Interest

The authors declare that there is no conflict of interest.

ACKNOWLEDGMENT

The Authors Acknowledge Mohamed Sathak A.J.College of Pharmacy and JKKMMRFs Annai JKK Sampoorani Ammal College of Pharmacy, for providing supports and facilities to conduct the research.

REFERENCES

1. Ozougwu JC. Physiology of the liver. International Journal of Research in Pharmacy and Biosciences. 2017 Jan 1;4(8):13-24.
2. Garcia-Cortes, M., Robles-Diaz, M., Stephens, C., Ortega-Alonso, A., Lucena, M.I. and Andrade, R.J. Drug induced liver injury: an update. Archives of Toxicology. 2020;94(10):3381-3407.
3. O'connor N, Dargan PI, Jones AL. Hepatocellular damage from non-steroidal anti-inflammatory drugs. Qjm. 2003 Nov 1;96(11):787-91.
4. Mahadevan SB, McKiernan PJ, Davies P, Kelly DA. Paracetamol induced hepatotoxicity. Archives of disease in childhood. 2006 Jul 1;91(7):598-603.
5. Wang X, Wu Q, Liu A, Anadón A, Rodríguez JL, Martínez-Larrañaga MR, Yuan Z, Martínez MA. Paracetamol: overdose-induced oxidative stress toxicity, metabolism, and protective effects of various compounds in vivo and in vitro. Drug metabolism reviews. 2017 Oct 2;49(4):395-437.
6. Algren DA. Review of N-acetylcysteine for the treatment of acetaminophen (paracetamol) toxicity in pediatrics. InSecond Meeting of the Subcommittee of the Expert Committee on the Selection and Use of Essential Medicines Geneva 2008 Sep 29 (Vol. 29).
7. MANNS MP. Recent developments in autoimmune liver diseases. Journal of gastroenterology and hepatology. 1997 Oct;12(9-10):S256-71.
8. Shirani M, Raeisi R, Heidari-Soureshjani S, Asadi-Samani M, Luther T. A review for discovering hepatoprotective herbal drugs with least side effects on kidney. Journal of nephropharmacology. 2017 Feb 21;6(2):38-48.
9. Lam P, Cheung F, Tan HY, Wang N, Yuen MF, Feng Y. Hepatoprotective effects of Chinese medicinal herbs: a focus on anti-inflammatory and anti-oxidative activities. International Journal of Molecular Sciences. 2016 Mar 29;17(4):465.
10. Bhardwaj N, Tripathi N, Trivedi R, Kumar D, Ravikanth G, Jain SK. Phytochemical Analysis, Cytotoxic Evaluation, and In Silico Screening of Metabolites From Dysoxylum malabaricum Bedd. Chemistry & Biodiversity. 2025 Mar 5:e202403419.
11. Najmuldeen IA, Ketuly KA, Hadi AH. Phenolic compound, triterpene and steroids from the leaves and bark of Dysoxylum macrocarpum. Science Journal of University of Zakho. 2013 Jun 30;1(1):227-45.
12. Hisham A, Bai MA, Jayakumar G, Nair MS, Fujimoto Y. Triterpenoids from Dysoxylum malabaricum. Phytochemistry. 2001 Feb 1;56(4):331-4.
13. Zhou MM, Zhang WY, Li RJ, Guo C, Wei SS, Tian XM, Luo J, Kong LY. Anti-inflammatory activity of Khayandirobilide A from Khaya senegalensis via NF-κB, AP-1 and p38 MAPK/Nrf2/HO-1 signaling pathways in lipopolysaccharide-stimulated RAW 264.7 and BV-2 cells. Phytomedicine. 2018 Mar 15;42:152-63.
14. Uddin SJ, Nahar L, Shilpi JA, Shoeb M, Borkowski T, Gibbons S, Middleton M, Byres M, Sarker SD. Gedunin, a limonoid from Xylocarpus granatum, inhibits the growth of CaCo-2 colon cancer cell line in vitro. Phytotherapy Research. 2007 Aug;21(8):757-61.
15. Nathan SS, Kalaivani K, Sehoon K. Effects of Dysoxylum malabaricum Bedd.(Meliaceae) extract on the malarial vector Anopheles stephensi Liston (Diptera: Culicidae). Bioresource technology. 2006 Nov 1;97(16):2077-83.
16. Lin LJ, Huang XB, Lv ZC. Isolation and identification of flavonoids components from Pteris vittata L. SpringerPlus. 2016 Sep 23;5(1):1649.
17. Avinash Kumar Reddy, G., Trilok Mitra, M., Shilpa, T., Shabnam, S., Satish Babu, K., Jyothi M Joy. Variation of Phenols, Flavonoids and Antioxidant Potential in Various Parts of Foeniculum vulgare on Drying. International

Journal of Chemical and Pharmaceutical Sciences. 2012;3(1):74-79.

18. Salem GA, Shaban A, Diab HA, Elsaghayer WA, Mjedib MD, Hnesh AM, Sahu RP. Phoenix dactylifera protects against oxidative stress and hepatic injury induced by paracetamol intoxication in rats. Biomedicine & Pharmacotherapy. 2018 Aug 1;104:366-74.

19. Lodhi P, Tandan N, Singh N, Kumar D, Kumar M. Camellia sinensis (L.) Kuntze Extract Ameliorates Chronic Ethanol-Induced Hepatotoxicity in Albino Rats. Evidence-Based Complementary and Alternative Medicine. 2014;2014(1):787153.

20. Subramaniyan V, Middha A. Chronic ethanol consumption-induced hepatotoxicity and protective effect of Boswellia serrata. National Journal of Physiology, Pharmacy and Pharmacology. 2016;6(2):170.

21. Singh M, Wal P, Wal A, Srivastava S. Hepatoprotective Evaluation Of Bixa Orellana L. Seed Extract Against Acute Ethanol-Induced Hepatotoxicity In Rats. International Journal of Pharmaceutical Sciences and Research. 2018 Dec 1;9(12):5168-76.

22. Misra HP, Fridovich I. The role of superoxide anion in the autoxidation of epinephrine and a simple assay for superoxide dismutase. Journal of Biological chemistry. 1972 May 25;247(10):3170-5.

23. Claiborne AJ. Handbook of methods for oxygen radical research. Florida: CRC Press, Boca Raton. 1985:283-4.

24. Sahu BD, Kuncha M, Putcha UK, Sistla R. Effect of metformin against cisplatin induced acute renal injury in rats: a biochemical and histoarchitectural evaluation. Experimental and Toxicologic Pathology. 2013 Sep 1;65(6):933-40.

25. Parmar SR, Vashrambhai PH, Kalia K. Hepatoprotective activity of some plants extract against paracetamol induced hepatotoxicity in rats. J Herbal Med Toxicol. 2010;4(2):101-6.

26. Campbell I. Liver: metabolic functions. Anaesthesia & intensive care medicine. 2006 Feb 1;7(2):51-4.

27. Canbay A, Bechmann L, Gerken G. Lipid metabolism in the liver. Zeitschrift für Gastroenterologie. 2007 Jan;45(01):35-41.

28. Enjoji M, Kohjima M, Nakamuta M. Lipid metabolism and the liver. InThe liver in systemic diseases 2016 Jun 30 (pp. 105-122). Tokyo: Springer Japan.

29. Abenavoli L, Milic N. Silymarin for liver disease. InLiver pathophysiology 2017 Jan 1 (pp. 621-631). Academic Press.

30. Zhu R, Wang Y, Zhang L, Guo Q. Oxidative stress and liver disease. Hepatology Research. 2012 Aug;42(8):741-9.

31. Mohi-Ud-Din R, Mir RH, Sabreen S, Jan R, Pottoo FH, Singh IP. Recent insights into therapeutic potential of plant-derived flavonoids against cancer. Anti-Cancer Agents in Medicinal Chemistry-Anti-Cancer Agents). 2022 Dec 1;22(20):3343-69.

32. Mochahary B. *Scientific Validation Of The Formulation And Evaluation Of Polyherbal Dosage For Hepatoprotective Active Activity Prescribed By The Local Medicinal Practitioner Of Btr, Assam, India* (Doctoral Dissertation, Dept Of Biotechnology).

33. Fu K, Wang C, Ma C, Zhou H, Li Y. The potential application of Chinese medicine in liver diseases: a new opportunity. Frontiers in Pharmacology. 2021 Nov 4;12:771459.

34. Li X, Li S, Li N. Research Progress on Natural Products Alleviating Liver Inflammation and Fibrosis via NF-κB Pathway. Chemistry & Biodiversity. 2025 Apr;22(4):e202402248.

35. Sharma NK, Bahot A, Sekar G, Bansode M, Khunteta K, Sonar PV, Hebale A, Salokhe V, Sinha BK. Understanding cancer's defense against topoisomerase-active drugs: A comprehensive review. Cancers. 2024 Feb 6;16(4):680.