



Lipid Lowering and Hepatoprotective Activity of *Premna Tomentosa* Leaf Extract (EPT) against Alcohol Induced Toxicity in Rats

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Abstract: The present study aims to determine the hepatoprotective and lipid lowering property of ethanolic leaf extract of *Premna tomentosa* (EPT) in alcohol induced hepatotoxicity. Chronic ethanol consumption is a significant danger factor in deciding liver disorders and other metabolic conditions through various mechanisms, including the regulation of the lipid metabolism. Medicinal plants are accepted to be a significant wellspring of new chemical substances with expected remedial impacts. *Premna tomentosa* (Verbenaceae) is a popular medicinal plant used extensively for the treatment of various ailments widely used in liver disorders. In the present research study, the male albino Wistar rats were grouped (I-V) each consisting of 6 animals. In-vivo administration of 40 % ethanol (1 ml/100 gm b w/day) for 60 days resulted in a significant elevation in Total cholesterol, Triglycerides, LDL, and VLDL levels whereas the levels of HDL was found to be decreased when compared with the control rats. Liver tissues disclose central vein and sinusoidal capillary dilation, interface hepatitis, cytoplasmic vacuolization and mononuclear cell infiltration which confirms the intensity of liver damage due to chronic alcohol ingestion. Simultaneous EPT supplementation (500mg/kg and 750 mg/kg bw) to alcohol -intoxicated rats, reduced the levels of Total cholesterol, triglycerides, and lipoproteins consequential as analogized with the unsupplemented alcohol- treated rats. Liver of rats pre-treated with ethanolic extract of *Premna tomentosa* (500 mg and 750 mg) manifest reduced formation of interface hepatitis, vascular congestion, and fatty degeneration and exhibits more hepatoprotection compared with the rats pre-treated in Liv 52. The blood parameters were amplified by the histopathological perusal of the liver. The lipid -lowering property by the derivatives of cinnamic acid showed anticholesteremic activity. The results confirm the Hepatoprotective and lipid -lowering ability of *Premna tomentosa* in alcohol-treated rats.

Keywords: Alcohol; Hepatotoxicity; H&E stain; Lipid profile; Liver; *Premna tomentosa*.

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I. INTRODUCTION

Ethanol is an amphipathic agent that affects almost all organs of the body as it can permeate all tissues and is soluble both in water and lipids, so excessive ethanol intake leads to Alcoholic liver diseases, gastrointestinal disorders, immune system dysfunction, cardiovascular diseases and malignant tumour¹. Chronic administration of ethanol has been known to cause marked alteration in lipid and lipoprotein metabolism. The organ solely present in the body for cholesterol disposition, via bile acids synthesis and excretion is liver². In hepatocytes excessive triglyceride accumulation due to alcohol abuse is the initial stage of the disease spectrum of alcoholic liver disease, it also plays a significant role in the disease advancement to late-stage hepatitis and/or cirrhosis³. Steatosis, inflammation, necrosis, fibrosis and finally cirrhosis characterize the progression of alcoholic liver disease⁴. When severe hepatitis occurs, death is the outcome⁵. Alcoholic liver injury emerges to be generated by the effects of ethanol metabolism and the toxic effects of the immune response to alcohol or acetaldehyde altered proteins. The three main pathways hepatocytes contain for ethanol metabolism to give acetaldehyde, each located in a different subcellular compartment namely, the alcohol dehydrogenase pathway of cytosol, the microsomal ethanol oxidizing pathway located in the endoplasmic reticulum and catalase pathway located in the peroxisomes. Due to several undesirable effects of synthetic drugs, the world population is turning toward medicines derived from locally available plants or native extracts of edible plant parts. Native plants have been the conventional wellspring of crude materials for the manufacture of medicines. The assorted culture of our nation is a rich wellspring of customary medicines, large numbers of which one of plant beginning logical information on such plant subsidiaries could be of clinical significance⁶. Because of the pitfalls of psychological dependence and destructive effects of synthetic drugs, the high efficiency and fewer side effects medicines derived from natural products exhibit expansive market prospects. Natural antioxidants of plant origin have more noteworthy application and they can likewise be utilized as nutraceuticals and phytochemicals as they essentially impact on human wellbeing and disease prevention⁷. Various medicinal plants such as *Eclipta prostrata*, *Emblin myrobalan*, *Phyllanthus niruri*, *Erythrina indica* etc., have shown good hepatoprotective property⁸. *Premna tomentosa* (Verbenaceae) is one such renowned ayurvedic herbal plant used broadly in the treatment of liver disorders. In the Indian system of medicine, all parts of *Premna tomentosa* have been utilised for the treatment of various disorders⁹. Tannins, phenolic compounds, alkaloids and flavonoids are the Phytochemical compounds present in the ethanolic extract of *Premna tomentosa* leaves with possible antioxidant activity¹⁰. Tannins are known to exert antihepatotoxic action¹¹. Extracts of *Premna tomentosa* leaves exhibit hepatoprotective, anti-inflammatory¹², antioxidant, diuretic, lipid-lowering¹³, cytoprotective, immunomodulatory activities, antinociceptive and protective effects on mitochondrial dysfunction

properties. The dried entire plant is used as a poultice to soothe skin irritation caused by caterpillars; the decoction of the leaf is extensively used to treat hemiplegia^{14,15,16}. The aim of this study was to investigate the lipid lowering and protective effects of ethanol leaf extract of *Premna tomentosa* in alcohol induced hepatotoxicity in male albino rats.

2. MATERIALS AND METHODS

2.1 Collection of Plant Material

Premna tomentosa leaves were freshly collected from SMPG, Mettur, Tamilnadu. Leaves were taxonomically identified and authenticated by Dr S. Sankara Narayana, HOD, Dept of Medicinal Botany, GSMS, Anna arch, Chennai and voucher No. GSMS/MB-Voucher Specimen No.23/2017.

2.2 Extract Preparation

2.2.1 Successive Soxhlet Extraction

The *Premna tomentosa* leaves were dried and coarsely powdered, then successive extraction was done using the Soxhlet apparatus with ethanol as solvent¹⁷. After each extraction, the solvent was recovered under reduced pressure using a rotary evaporator. This was followed by extract reconstitution with normal saline to standardize the extract (based on the weight of the laboratory animal used) to 750 and 500 mg/kg body weight doses.

2.3 Animals

Wister strain male albino rats weighing 150 -200 g body weight were used for the present study. The animals were redistributed into polypropylene cages (6 per cage) and observed under a 12-h light & dark cycle in a well-ventilated room and standard temperature (24± 2 °C), as well as humidity (60-70%), was maintained. They were fed with a standard diet and water ad libitum. The study was authorized by the Institutional Animal Ethical Committee of Swamy Vivekananda College of Pharmacy, Tamilnadu (Reg.No.889/PO/Re/S/05/CPCSEA / 2018).

2.4 EXPERIMENTAL PROCEDURE

Five groups of six rats each were used for the study. The Ethanolic Extract of *Premna tomentosa* (EPT) and alcohol was administered using intragastric lavage daily for 60 days.

Group I: Control Rats (1 ml/100 gm normal saline, b. wt. p.o).

Group II: Rats administered alcohol (40% Alcohol 1 ml/100 g b. wt. p.o).

Group III: Rats administered Liv 52 (1 ml/100 gm b. wt. p. o) along with 40% Alcohol 1 ml/100 g b. wt. p.o/day.

Group IV: Rats administered EPT (500 mg/kg b. wt. p. o) along with 40% Alcohol 1 ml/100 g b. wt. p.o/day.

Group V: Rats administered EPT (750 mg/kg b. wt. p. o) along with 40% Alcohol 1 ml/100 g b. wt. p.o/day.

2.5 Biochemical Analysis

The blood samples were collected from the retro-orbital plexus and processed. The sera were separated for estimation of biochemical parameters i.e., Estimation of Total

Cholesterol, Triglycerides, HDL, VDL and VLDL. After completion of experimental duration, the animals were sacrificed by overdose of diethyl ether.

2.6 Histological Analysis

For histopathologic studies, the liver was excised from the rats, and immersed in 10% formalin for 24 h for fixation, followed by embedding in paraffin wax and sliced into 5-micron thickness using microtome¹⁸. The slices were mounted on the glass slides and stained with haematoxylin and eosin. (H and E). These slides were examined using Leica Dmd 360 Microimaging Camera, German, Photomicroscopy.

3. STATISTICAL ANALYSIS

All results were expressed in terms of Mean \pm S.E.M. The difference between groups was compared by one-way ANOVA followed by post hoc Duncan's multiple range test, using SPSS 21 software. $p < 0.05$ were considered significant.

4. RESULTS

4.1 Biochemical Parameters

Table I shows the concentration of serum Total cholesterol and Triglycerides in control and experimental rats. In alcohol rats (Group II), there was a remarkable increase in Total Cholesterol and Triglycerides when compared with control rats (Group I). Rats was administered with extract of *Premna tomentosa* (750 mg/kg b. wt. p. o) along with 40% Alcohol I ml/100 g b. wt (Group V) shows significantly lower levels of Total Cholesterol and Triglycerides compared with Alcohol rats (Group II). Rats pre-treated with extract of *Premna tomentosa* EPT (500 mg/kg b. wt. p. o) along with 40% Alcohol I ml/100 g b. wt. (Group IV) and Group V manifest similar results which were marginally lower than Rats administered Liv 52 (1 ml/100 gm b. wt. p. o) along with 40% Alcohol I ml/100 g b. wt. (Group III). Graph I shows the values of serum HDL, LDL and VLDL levels in control and experimental groups. LDL, VLDL concentration was significantly increased and HDL values were remarkably decreased in alcohol rats (Group II) when compared with control rats (Group I). Upon treatment of extract of *Premna tomentosa* (Group IV & Group V) at various doses, there was a remarkable elevation in HDL and decrease in LDL and VLDL levels compared with the alcohol group (Group II). These parameters were reversed back to normal levels following *Premna tomentosa* treatment. Liv 52 treated rats (Group III) show significant changes in lipid profile when compared to alcohol-treated rats (Group II).

4.2 Histopathological Examination

Control rats (Fig 1.1) show normal central vein and sinusoidal capillary size with no evidence of congestion or narrowing and normal hepatocyte without any changes in their cytoplasm and nucleus Fatty infiltration in all ethanol-fed rats (fig 1.3) is observed with altered architecture with bile duct hyperplasia, central vein and sinusoidal capillary dilation, portal tract with sinusoidal congestion (fig 1.2). and mononuclear cell infiltration (fig 1.4). Rats pre-treated with Liv 52 (fig 1.5) shows normal hepatic architecture with tiny cytoplasmic vacuoles and sinusoidal dilatation. Fig 1.6 and 1.7 shows liver changes in rats pre-treated with EPT 500 mg/kg

and EPT 750 mg/kg with mild congestion of central vein and mild altered lobular architecture.

5. DISCUSSION

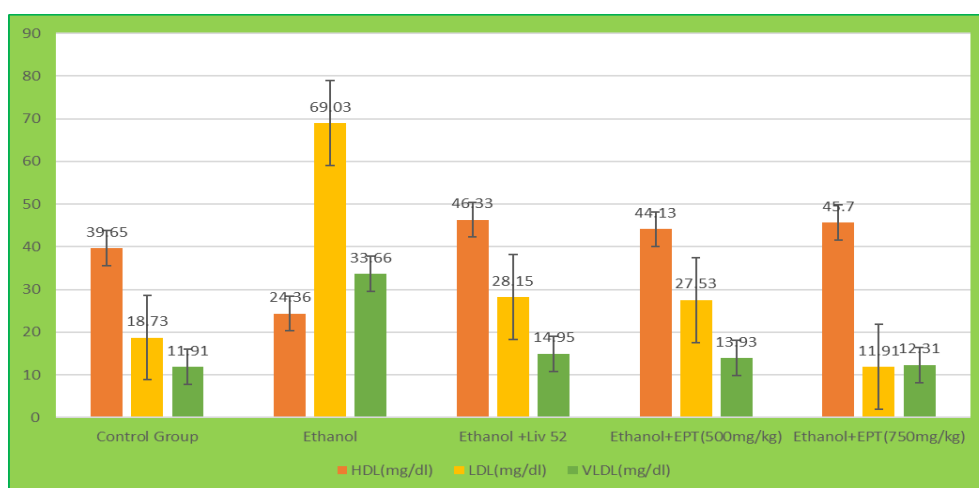
Recognition of an association between alcohol and coronary disease has led to an increasing interest in alcohol-induced changes in lipids and lipoproteins. Roughly about 90% of the alcohol is metabolized in the liver and gastrointestinal tract, lungs, and kidneys play only a minor role¹⁹. Blood cholesterol may be conveyed to the liver by LDL through the LDLR of hepatocytes. The greater part of cholesterol retained in food is transported into the liver as LDL-c. At the point when the LDLR increases, more cholesterol is moved into the liver, consequently causing more extreme hepatic cholesterol accumulation²⁰ and enhanced lipid peroxidation. ²¹The biologically active components found in *Premna tomentosa* leaf sparing the antioxidant activity and deteriorate the consumption of endogenous antioxidants, which could be responsible for the depletion of oxidative stress during ethanol toxicity²². Gomathi Priyadharsini et al., reported the presence of active constituents such as alkaloids, flavonoids, tannins, steroids and phenolic compounds in *Premna tomentosa*¹⁰ and it has been reported as powerful antioxidants²³. Previous literature has shown that phenolic compounds can standardize the levels of tissue lipids during diseased conditions^{24,25}. The phenolic compound present in EPT might be responsible to reduce the lipids in the ethanol-fed rats co-treated with EPT ²⁶. Rahman et al stated that overall mild raised total cholesterol, serum triglyceride; VLDL, LDL values and lowered HDL were noted in the alcoholic group as compared to the non-alcoholic group. Highly statistically significant values were noted in HDL values²⁷. Chander et al states Chronic administration of ethanol in rats caused the reduction of serum cholesterol-binding reserve. The very low density and high-density lipoproteins, main serum cholesterol-binding reserves, were increased mildly with analogous increases in their lipid and protein components during the beginning phase of alcohol consumption. However, these limits get diminished during reversal of hyperlipemia actuated by prolonged action of ethanol which may be an early indicator for the commencement of hepatic damage and a variety of secondary effects of ethanol²⁸. Alcohol consumption stimulates the hepatic secretion of VLDL, possibly by inhibiting the hepatic oxidation of free fatty acids, which then stimulate hepatic triglyceride synthesis and VLDL secretion²⁹. In the present study alcohol-induced hyperlipidemia is evidenced by significant elevation in the levels of serum Total cholesterol, triglycerides, LDL, VLDL and eventual diminishing in the level of HDL. This elevated concentration of LDL in the alcohol-treated rats might be due to a defect in the LDL receptor either through failure in its production (or) function. HDL is protective by reversing cholesterol transport, inhibiting the oxidation of LDL and neutralizing the atherogenic effects of oxidized LDL. A greater increase of LDL and VLDL might have been due to reduction in the level of HDL and diminished lecithin cholesterol acyl transferase activity³⁰. Fernandez-Martinez et al state that the role of hepatoprotective property is because of the presence of Hydroxycinnamic acid and halogenated cinnamic acid and 3-phenyl propionyl moiety will result in antimalarial activity³¹. Chronic ethanol administration in rodents produces several hepatic changes, including hepatocellular necrosis³², mono or poly inflammatory cell infiltration and sinusoidal

dilation with congestion³³. Hassan et al mentioned Rodents exhibit, terminal hepatic venular sclerosis³⁴ and tumour development in chronic ethanol administration³⁵. Pre-treatment of rats with 750 mg/kg bw ethanolic extract of *Premna tomentosa* was more effective in protecting rats against necrosis, interface hepatitis and thrombosis due to

chronic congestion when compared with 500 mg/kg bw ethanolic extract of *Premna tomentosa*. Regeneration of cells and morphological changes in the accumulation of fats was increased by pretreating with *Premna tomentosa* extract as well as pre-treatment with Liv 52.

Table 1: Effect of Pre-treatment with <i>Premna tomentosa</i> (EPT) and alcohol on Total Cholesterol and Triglycerides of control and experimental rats		
Groups	Total Cholesterol (mg/dl)	Triglycerides(mg/dl)
Control	81.83±1.76	127.38 ±1.90
Ethanol	290.83 ±10.79 **	167.01±4.11 **
Ethanol + Liv 52	100.41±3.63 **	135.13±2.99 **
Ethanol+ EPT (500 mg/kg)	95.75±1.51 **	126.38±4.24 **
Ethanol +EPT (750 mg/kg)	89.15±2.00 **	122.8±6.24 **

Effect of the EPT on Total cholesterol level and Triglycerides of normal and alcohol induced hepatotoxicity rats, values are Mean ± S. D values of 6 animals each, **p<0.001, *p<0.01, p > 0.05 ns - non significant; ethanol group was compared with the control, EPT (500 & 750 mg/kg b. wt.) and standard treated groups were compared with the ethanol group.



Graph 1: Result of EPT and alcohol on HDL, LDL, VLDL levels of control and experimental rats

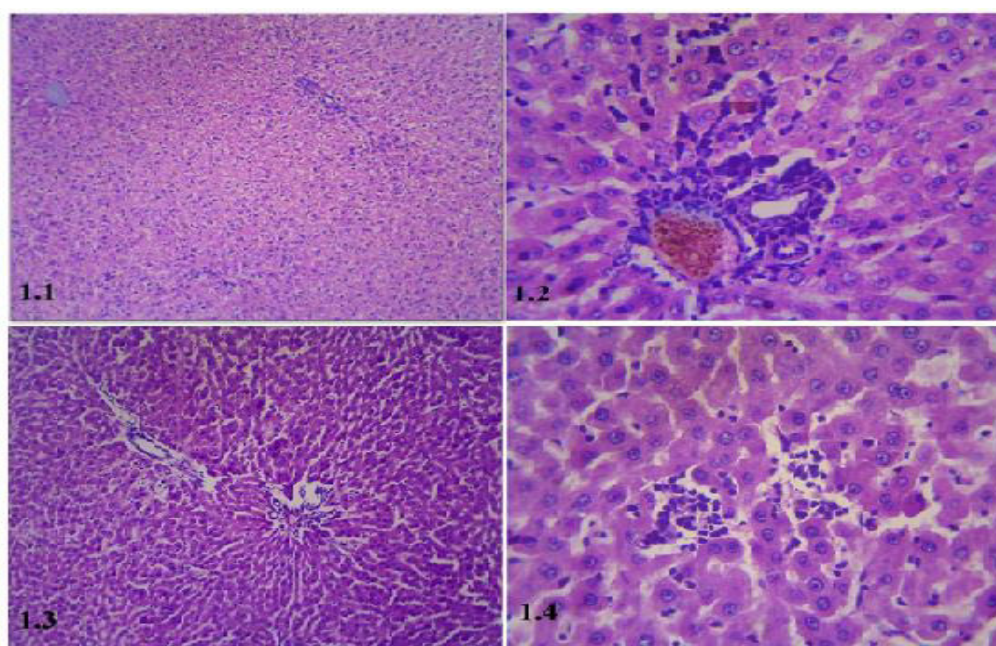


Fig 1.1 control group: shows normal central vein, sinusoidal capillary, hepatocytes and portal tract, Fig 1.2-1.4 Alcohol group: shows portal tract with sinusoidal congestion (1.2), central vein and sinusoidal capillary dilation, cytoplasmic vacuolation and interface hepatitis (1.3), mononuclear cell infiltration (1.4).

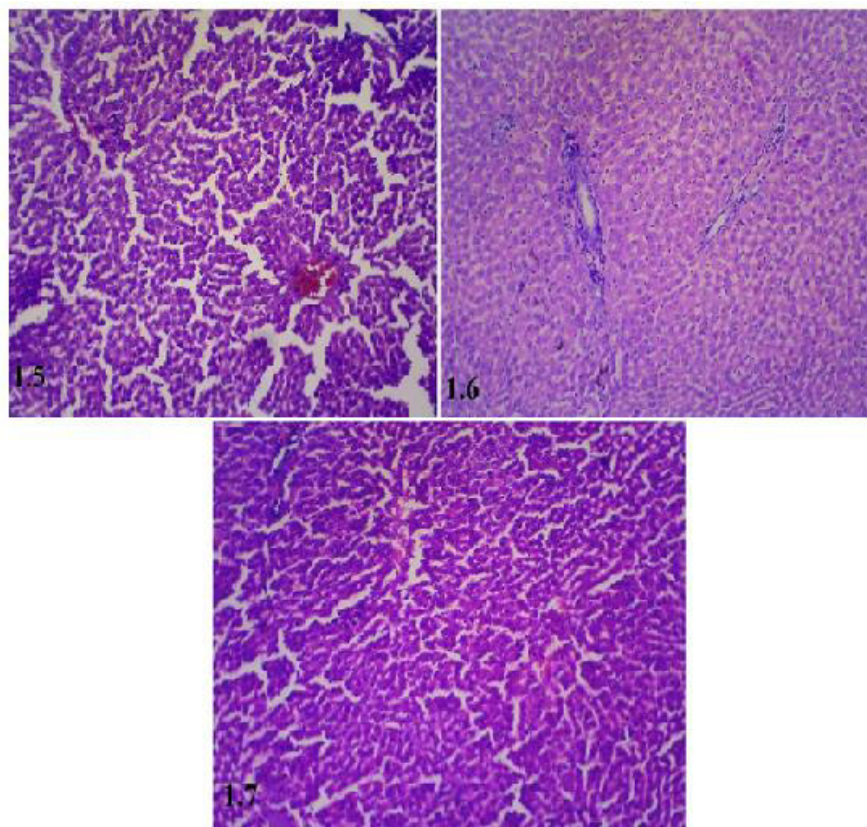


Fig 1.5 Liv 52 group: shows mild altered lobular architecture, Fig 1.6 EPT (500 mg/kg) group: shows swollen hepatocytes with decreased sinusoidal spaces, Fig 1.7 EPT 750 mg/kg group: shows normal hepatic parenchyma with mild degenerations.

6. CONCLUSION

From the current study, ethanol leaf extract of *Premna tomentosa* showed significant elevation in the levels of serum total cholesterol, triglycerides, LDL, VLDL and eventual diminishing in the level of HDL. It may be concluded that *Premna tomentosa* leaf extract (EPT) can be used as lipid lowering supplement and has remarkable hepatoprotective activity in attenuation of pathological changes in liver tissues. The present study opens many new areas of research work. This work can be continued in future to study and confirm liver protective activity in different models.

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7. AUTHORS CONTRIBUTION STATEMENT

Dr.T. Gomathi Priyadharsini, who is the principal investigator of this work, has contributed to data collection, processing and interpretation of results. Dr. M. Kavimani, Research Guide has given valuable inputs, suggestions and guidance for the successful completion of this work and in designing the manuscript. All the authors read and approved the final version of the manuscript.

8. CONFLICT OF INTEREST

Conflict of interest declared none.

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