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Evaluation of Hepatoprotective Activity of *Pachyrhizus Erosus*, extract against Paracetamol Induced Hepatic Damage in Rats

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ABSTRACT

Pachyrhizus Erosus (family: Fabaceae) has been traditionally used in Indian medicine as a result of its curative results of hepatitis, gonorrhea and diabetes. No systemic study has been done on protective effect of Pachyrhizus Erosusto treat hepatic diseases. So claims can be made for the protective efficacy of Pachyrhizus Erosus to treat hepatic diseases. The present study focused on investigating the role of methanolic extract of Pachyrhizus Erosus (MEPE). MEPE at a dose level of 250mg/kg b.wt/day p.o and 500mg/kg b.wt/day p.o produce significant ($P<0.05$) hepatoprotection by decreased the level of serum Aspartate amino transferase (AST), Alanine amino transferase (ALT), alkaline phosphatase (ALP) and Total serum bilirubin (SB), while they significantly increased the level of glutathione (GSH)in a dose dependent manner. The effects of MEPE were comparable to that standard drug, silymarin. Histopathological observations confirmed the beneficial role of MEPE against Paracetamol (PCM) - induced liver injury in rats. The result suggests that the methanolic extract of Pachyrhizus Erosus possess significant potential as hepatoprotective agents.

***Key words**: Hepatoprotective, Pachyrhizus Erosus, Paracetamol, Lipid Peroxidation, Glutathione*

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1. INTRODUCTION:

*Pachyrhizus Erosus*is an annual herb belongs to the family Fabaceae [1] which mainly occurs in India, W. Peninsula, China and Ceylon. In India it is found in Andhra Pradesh and Tamil Nadu[1]. *Pachyrhizus Erosus* has been frequentlyused as an alternative, astringent to the bowels, worms, itching, useful in gonorrhea[1, 2]. The juice of the leaves of the plant is used for the treatment of diabetes, cures ulcers and traditionally used for the treatment of antioxidant [2-4].Since no scientific data are available to justify the traditional hepatoprotective potential of the plant.

Acetaminophen (N-acetyl-p-aminophenol, Paracetamol) is usually used as an analgesic and antipyretic drug [5]. Extensive use of PCM for therapeutic functions leads to severe hepatic damage. Toxic doses of PCM could induce changes in the morphology and function of liver mitochondria[6]. Formation of N-acetyl-p-benzoquinone imine (NAPQI) is the responsible for liver injury through depletion of glutathione (GSH) even as it binds to cellular proteins[7]. PCM induced hepatotoxicity is known to involve liver cytochrome P_{450} (CYPs) together CYP2E1, CYP3A4, and CYP1A2 and it also inhibits the mitochondrial oxidative phosphorylation, reduction of adenosine triphosphate (ATP) and produces selective mitochondrial oxidant stress[8]. Cellular necrosis of the liver cells raises the lipid peroxidation and depletion of glutathione (GSH) besides elevating the serum biochemical marker levels [5].

The survey of literature reveals that the *Pachyrhizus Erosus* are found to be used in the traditional system of medicine as a liver tonic[2]. However, hepatoprotective activity of *Pachyrhizus Erosus* has not been scientifically investigated. Therefore, in the present study hepatoprotective effect of methanolic extract of *Pachyrhizus Erosus* have been evaluated against paracetamol induced liver damage in the wistar albino rats.

2. MATERIALS AND METHODS:

2.1. Chemicals:

Paracetamol 500 mg tablets (Nirmal Prime, Mumbai, India). Silymarin was purchased from Micro labs, Tamilnadu, India. Moreover, saline was purchased from GSN pharmaceutical private limited, Hyderabad, Telangana, India. The following biochemical parameters of AST, ALT, ALP and Bilirubin kits were obtained from Span Diagnostics, Surat, India. Rat's feed was once supplied from Mahaveer Endeavors, Medipally and Hyderabad, India. All other chemicals and reagents used in the study were of analytical grade.

2.2. Plant materials:

The plant of *Pachyrhizus Erosus* was collected from mature plant during the month of November from the wood's territory of the Tirumala Hills, Tirupathi, Chitoor district. Andhra Pradesh (India). The plant material was taxonomically identified by Dr. K. Madhava chetty, Department of Botany, Sri Venkateshwara University, Tirupathi, Andhra Pradesh, India and a specimen was kept in the herbarium. The plant materials were washed thoroughly to remove adhering soil and earthen matter, later on sliced into thin chips and dried in shade at room temperature and then after ground to optimal coarse powder.

2.3. Preparation of Extracts:

The powder (650 gm) was extracted at ambient temperature and 60ºC successively with (95% methanol). The solvent was changed at regular intervals of every 24 h. The alcohol from the pooled extractions were removed through distillation under reduced pressure at 50-60ºC to withstand MEPE (256g). The extracts were then subjected to preliminary phytochemical investigations and subjected for hepatoprotective activity against PCM-induced liver damage.

2.4. Preliminary Phytochemical Studies:

The extract of *Pachyrhizus Erosus* were subjected to preliminary phytochemical screening for the detection of various phytochemical constituents such as carbohydrates, proteins, amino acids, steroids, tannins, flavonoids, terpenoids, alkaloids, mucilage and glycosides, using standard procedure[9,10], to find out the nature of phytoconstituents present within them

2.5. Experimental animals:

An experimental study was carried out using Wister albino rats of either sex (male and female) rat's age two months. Their body weights ranged from 150 to 200 g. The rats were divided into 5 groups of 6 (3 male and 3 female) animals per cage was used. Animals were maintained under standard laboratory aseptic conditions (12-h light/dark cycle, 24hrs). The food in the form of dry pellets and water is provided *ad libitum*. All the animals were accepted by the ethics approval committee of the institute.

2.6. Paracetamol (PCM) Induced Liver Toxicity:

The paracetamol (PCM) was diluted with saline (vehicle) prior to oral administration (o.p). The group I: vehicle (saline) once daily for 9 days. Group II: vehicle + PCM (1 mL/kg, p.o) once daily for nine days. Group III: Silymarin (100 mg/kg b.wt/day, p.o) + PCM (1 mL/kg, p.o) once daily for nine days. Group IV: MEPE (250 mg/kg b.wt/day, p.o) + PCM (1

mL/kg, p.o) once daily for nine days. Group V: MEPE (500 mg/kg b.wt/day, p.o) + PCM (1 mL/kg, p.o) once daily for ninth day. To enhance the acute liver damage in animals of groups V, IV, III and II, food were withdrawn 12 h before PCM administration. Animals were sacrificed 24 h after administration of PCM. Blood samples were further collected and pooled by puncturing the retro-orbital plexus underneath using mild ether anesthesia and allowed to coagulate for 30 min at 37°C. Serum was isolated by centrifugation at 2500 rpm for 15 min at 35°C and further analyzed for various biochemical parameters [9-11].

2.7. Assessment of Liver Functions:

The hepatoprotective impact of extract was assessed by the measure of liver, biochemical markers. Alanine Amino Transferase (ALT)[14],Aspartate Amino Transferase (AST)[15] Alkaline Phosphatase (ALP) [16] and Total Serum Bilirubin (SB)[13], Lipid Peroxidation (LPO) as Malondialdehyde (MDA) [17] and Glutathione (GSH) [18] according standard methods. Histopathological assessment of liver damage was done by studying Haematoxylin and Eosin (H&E) stained slides of liver tissue, including cell necrosis, fatty changes and lymphocytes[19-21].

2.8. Measurement of Antioxidant Activity:

From all the experimental groups, liver was collected and rinsed with 0.15 M Tris-HCl (pH 7.4). A 10% w/v of liver homogenate was prepared in 0.15 M Tris-HCl buffer and processed for biochemical estimation of lipid peroxidation in the form of malondialdehyde (MDA) in the liver[22].A part of homogenate after precipitating protein was used for estimation of reduced glutathione (GSH) [18]. The rest of the homogenate was centrifuged at 1500 rpm for 15 min at 4^0C.

2.9. Determination of lipid peroxidation in liver homogenate[22]

To 0.5 mL of homogenate tissue, 0.6 mL reagent (N-methyl -2-phenylindole and acetonitrile; 3:1) 1ml BHT (butylatedhydroxyltoluene) were added, mixed well and centrifuged at 3000 rpm at 10 min and boiled for 1h at 45^0C, the tubes were then cooled at room temperature and measured absorbance (UV-spectrophotometer, model UV-1601, Shimazu Corporation, Kyoto, Japan) at 586 nm.

3.0. Determination of reduced glutathione (GSH)[18]**:**

Homogenate tissue (0.2 mL) was mixed with 3.0 mL precipitating reagent (1.67g potassium phosphate, 0.2g EDTA, 30g P-nitro benzyl chloride (PNBS) in 1 L of distilled water) was added, mixed thoroughly and kept for 5 min before centrifugation. To 2.0 mL of the filtrate and absorbance measured at 310 nm.

3.1. Statistical Analysis:

The data was represented as mean ± SEM. Results were analyzed statistical by one way ANOVA test followed by Dunnet's assessment test using orgipro (Version 7.0). The minimum level of significance was set at $P<0.05$.

3. RESULTS:

Preliminary phytochemical investigation revealed the presents of flavonoids, phenols, terpenoids and steroids in methanolic extract.

3.1. Paracetamol (PCM) Induced Liver Toxicity:

The results of hepatoprotective activity of MEPE on PCM treated rats are show in Table 1. The hepatic enzymes AST, ALT, ALP and SB in serum significantly ($P<0.001$) increased in PCM treated animals compared to normal control (group-I). The MEPE treatments (250 and 500mg/kg p.o) significantly ($P<0.05$, $P< 0.01$; respectively) the levels of hepatic enzymes when compared to PCM-treated animals. Silymarin (100mg/kg) - treated animals also show significant ($P<0.001$) the levels of hepatic enzymes when compared with to PCM-treated animals. There was significantly decreased ($P<0.001$) in the serum total serum albumin levels in PCM treated groups when as compared to the control groups, which was significantly ($P<0.001$) with treated of MEPE 500mg/kg b.wt/day and 250mg/kg b.wt/day, respectively.

Table 1: Effect of methanolic extraction of *Pachyrhizus Erosus* on ALT, AST, ALP and SB in PCM induced liver toxicity in rats

Treatment	Dose	ALT (U/L)	AST (U/L)	ALP (U/L)	SB (mg/dl)
Group-I Vehicle (saline)	1ml/kg	57±1.06	52±2.89	103.33±6.52	0.55±0.02
Group-II Control (PCM)	1 mg/kg	220.66±2.52[a]	190.33±3.02[a]	248.16±5.38[a]	2.03±0.17[a]
Group-III PCM+ Silymarin	100 mg/kg	172±1.75[***]	133.50±3.68[***]	198.5±3.83[***]	0.93±0.07[***]
Group-IV PCM+ MEPE	250 mg/kg	209± 2.95[**]	160.33±2.58[**]	228.63±6.42[ns]	1.07±0.06[***]

Group-V PCM+ MEPE	500 mg/kg	191.83±6.17***	142.16±4.66***	212.16±6.73*	0.99±0.156***

*Each value represents the mean ± SEM. n =6 number of animals in each group. [a]P<0.001 vs vehicle control, *P<0.05, **P<0.01, *** P<0.001, Compared to respective PCM treated control groups*

3.2. Effect of *Pachyrhizus Erosus* on antioxidant activity:

There was a significant increase in MDA content and decrease in GSH activities of PCM intoxicated animals. Pre-treatment with silymarin (100 mg/kg b.wt/day) and *Pachyrhizus Erosus* (250 and 500 mg/kg p.o) significantly *P*< 0.05 prevented the increase in MDA levels and brought them near to normal level, whereas GSH levels were significantly (*P*< 0.001) raised, thus providing protection against paracetamol toxicities.Results are given Table 2.

Table 2: Effect ofmethanolic extraction of *Pachyrhizus Erosus* on lipid peroxidation (LPO), glutathione (GSH), PCM induced hepatic damage in rats

GROUP	DOSE	LPO (nM MDA/mg protein)	GSH (µg/mg protein)
Group-I Vehicle (saline)	1ml/kg	0.93±0.03	6.17±0.24
Group-II Control (PCM)	1ml/kg	4.18±0.18[a]	2.26±0.30[a]
Group-III PCM+ Silymarin	100 mg/kg	2.11±0.22***	5.01±0.10***
Group-IV PCM+ MEPE	250 mg/kg	2.21±0.11***	4.30±0.17***
Group-V PCM+ MEPE	500 mg/kg	2.55±0.23***	4.94±0.06***

*Each value represents the mean ± SEM. n =6 number of animals in each group. [a]P<0.001 vs vehicle control, *P<0.05, **P<0.01, *** P<0.001, Compared to respective PCM treated control groups*

3.3. Histopathological examination of rat livers:

On the ninth day, later the animals were sacrificed and liver tissues were gathered. In this study, histopathological observation of liver was performed to further support the biochemical analysis evidence. The model group revealed the most severe damage of all the groups; Microscopic view of liver tissue of silymarin and methanolic extracts of *Pachyrhizus Erosus* on ALT, AST, ALP and SB in PCM induced liver toxicity in rats rat. However, histological changes in liver tissues from groups which treated at dose 250 and 500 mg/kg p.o. (Fig 1A- E).

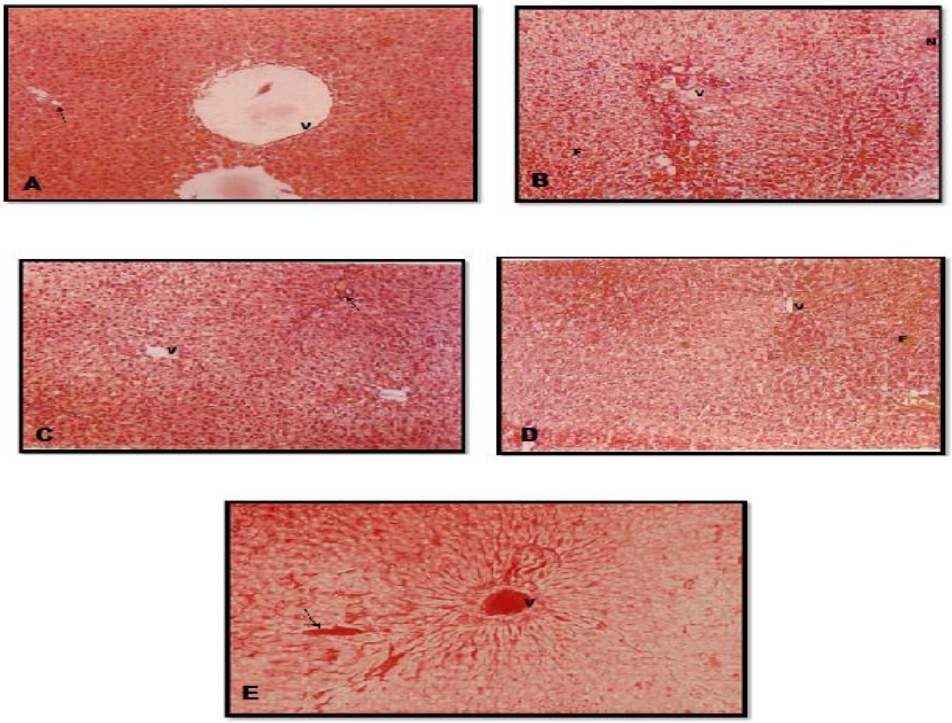

Figure 1:A) Microscopic view of liver tissue of normal rats; (B) Microscopic view of liver tissue of PCM; (C) Microscopic view of liver tissue of PCM + Silymarin; (D) Microscopic view of liver tissue of PCM + 250 mg/kg, po plant extract, (E) Microscopic view of liver tissue of PCM + 500 mg/kg, po plant extracts

Figure A: Liver tissues of control animal showing normal histology, section of normal liver tissue with portal triad showing portal vein (V), portal artery (arrow) and hepatic ducts (arrow head). Stain H and E, magnification 100X (Group I); Figure B: Liver tissue of animal treated with PCM showing necrosis, section of live tissue of animal treated with PCM showing necrosis (N), fatty vacuole (F) and central vein (v). Stain H and E, magnification 100x (Group II); Figure C: Liver tissue of PCM + Silymarin treated animals showing normal hepatocytes, section of normal liver tissue with portal triad showing portal vein (V), portal artery (arrow) and hepatic ducts (arrow head). Stain H and E, magnification 100X (Group III); Figure D: Liver tissue of PCM + 250 mg/kg b.wt, poMEPE showing normal arrangement of hepatocytes, section of the liver tissue of PCM + 250 mg/kg b.wt, po MEPE treated animals showing normal arrangement of hepatocytes around the portal vein (V), absence of necrosis and moderate accumulation of fatty vacuoles (F). Stain H and E, magnification 100X(Group IV); Figure E: Liver tissue of PCM + 500 mg/kg b.wt, po CETPF showing normal arrangement of hepatocytes, Section of the liver tissue of PCM + 500 mg/kg b.wt, poMEPE treated animals showing normal arrangement of hepatocytes around the portal vein (V), portal artery (arrow) and hepatic ducts (arrow head). Stain H and E, magnification 100X(Group-V)

4. DISCUSSION:

The *Pachyrhizus Erosus* extract has been reported to contain different types of terpenoids, the phytochemical screening. A number of compounds belonging to the class of polyphenol have been suggested to possess antioxidant and hepatoprotectiveactivitys[23]. Extensive liver damage by paracetamol itself decreases its rate of metabolism and other substrates for hepatic microsomal enzymes[24]. Interestingly the induction of cytochrome P_{450} or depletion of hepatic glutathione is a prerequisite for paracetamol-induced toxicity[25, 26].The hepatoprotective activity of *Pachyrhizus Erosus* (500 mg/kg, p.o and 250mg/kg p.o) was compared with the activity of standard silymarin (a hundred mg/kgb.wt/day). Pretreatment of animals with methanolic extracts of *Pachyrhizus Erosus* and silymarin prevented the Paracetamol induced rise in serum level of transaminases and total serum bilirubin, confirming the protective effects of methanolicextract of *Pachyrhizus Erosus* against Paracetamol induced hepatic damage.

However, there was no significant effect on rise in serum alkaline phosphatase levels by the test extract and silymarin. However the paracetamol induced liver necrosis was once inhibited significantly by using *Pachyrhizus Erosus* extract, which confirms the protective action of methanolic extract of *Pachyrhizus Erosus* against experimentally induced liver damage in rats. ALT, AST, ALP and SB are the most sensitive tests employed in the diagnosis of hepatic disease. Therefore it can be concluded from this investigation that extract of *Pachyrhizus Erosus* possess hepatoprotective activity. Further, detailed studies are warranted to confirm the utility profile of this drug.

CONCLUSION:

In conclusion, the result of this study demonstrates that *Pachyrhizus Erosus* has potent hepatoprotective action upon paracetamol-induced hepatic damage in rats. The present study thus justifies the traditional use of *Pachyrhizus Erosus* in treatment of liver diseases and also points out that *Pachyrhizus Erosus* warrants future detailed investigation as a promising hepatoprotective agent. However, the exact mechanism(s) and the active compound(s) involved in these effects need to be clarified in future studies.

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