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Research Article

NEPHROPROTECTIVE EFFECT OF ELSHOLTZIA BLANDA BENTH. IN PARACETAMOL INDUCED TOXICITY IN ALBINO RATS

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ABSTRACT

Paracetamol (PCM) is a commonly used analgesic antipyretic drug. Overdose can lead to nephrotoxicity and other organ damage. The study was conducted to evaluate the protective role of methanolic extract of *Elsholtzia blanda* Benth.(MEEB) in paracetamol induced nephrotoxicity in albino rats models. 30 albino rats were divided into 5 groups of six animals each. Study was conducted for 7 days and drugs were administered orally as : Group I- normal saline; II- PCM 2g/kg on day 7; III- silymarin 25mg/kg+PCM as in group II; IV- 200mg/kg of MEEB+PCM as in group II; V- 400mg/kg of MEEB+ PCM as in group II. Pretreatment with the plant extract could prevent the PCM induced renal damage as evidenced by the significant ($p<0.05$) reduction in serum creatinine and urea levels. There was a significant ($p<0.05$) increase in the serum albumin levels as compared to the toxic control group. Histopathological examination also showed less structural damage in the kidneys of extract treated animals. In conclusion, *Elsholtzia blanda* has a nephroprotective effect which could be attributed to its antioxidant properties.

INTRODUCTION

Drug-induced nephrotoxicity is a significant contributor to kidney disease. Prospective cohort studies of acute kidney injury (AKI) have documented the frequency of drug-induced nephrotoxicity to be approximately 14-26% in adult populations (Awdishu L and Mehta RL, 2017).

Paracetamol (PCM) is one of the most commonly used analgesic–antipyretic drugs worldwide for a variety of ailments. Overdose can lead to hepatic and renal toxicity. Renal insufficiency is reported to occur in 1–2% of patients exposed to paracetamol toxicity **(**Prescott LF, 1983**).** *N*-acetyl-*p*-benzoquinoneimine (NAPQI) is a reactive metabolite of PCM which is detoxified by intracellular glutathione (GSH). An overdose of PCM will saturate the conjugation pathways of GSH. Increased level of NAPQI mediates oxidative damage, and thus enhances cellular injuries and organ dysfunction, including renal damage (Hart SE *et al*, 1994).

Elsholtzia blanda Benth. (Family: *Lamiaceae*) is an aromatic shrub found in South West China, Myanmar, Central and Eastern Himalayas and the Northeastern states of India (Rana V *et al*, 2012). It has been traditionally used for wound healing, cough, dyspepsia, hepatitis, dysentery, tonsillitis, toothache, acute gastroenteritis, acute and chronic pyelonephritis (Srivastava RC, 2009; Singh HB, 2003; Liu A *et al*, 2007). Previous studies about the plant have reported the presence of flavones (Weiling Z *et al*, 1999), C-methylated flavones (Zheng S *et al*, 2001), linalool (Bestmann H *et al*, 1992), phenols and tannins (Khomdram SD and Singh PK, 2011). Various other studies have also found that the plant extract has antioxidant, antibacterial (Ishwori L *et al*, 2014; Zuo GY *et al*, 2008) and cardioprotective (Haiyun L *et al*, 2004) properties.

In this study, the renoprotective effect of the methanolic extract of *E. blanda* (MEEB) was studied using PCM induced nephrotoxicity. The effects were determined by measuring the levels of serum creatinine, urea, albumin levels and also by histopathological examination of kidney tissues.

MATERIALS AND METHODS

Plant materials and extraction

Fresh aerial parts of *E.blanda* were collected from Imphal West District of Manipur and authenticated in the Department of Life Sciences, Manipur University. The plant parts were then shade

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dried and methanolic extract was made using Soxhlet apparatus. The yield obtained was 6%.

Animals

The study was conducted in the Department of Pharmacology and Department of Pathology, RIMS, Imphal. The experimental protocol was approved by Institutonal Animal Ethics Committee (IAEC) of RIMS, Imphal (1596/GO/a/12/CPCSEA). 30 healthy albino male rats were obtained from the Central Animal House. Animals were then housed in a controlled environment with room temperature and a 12-h light-dark cycle. They were fed mouse pellet and fresh water ad libitum for 7 days prior to experiment. Rats were randomly divided into five groups of 6 animals each and study was conducted for 7 days.

Experimental design

Group 1 (normal control) received normal saline 5ml/kg orally for 7 days. Group 2 (nephrotoxic control) were given paracetamol (2g/kg) per orally on 7th day. Group 3(standard) received the standard drug silymarin (25mg/kg) per orally for 7 days and paracetamol (2g/kg) on 7th day whereas Group 4(test 1) and Group 5 (test 2) received 200mg/kg and 400mg/kg of methanolic extract of *Elsholtzia blanda* Benth. (MEEB) p.o. respectively for 7 days followed by paracetamol (2g/kg) on the last day.

Collection of blood and tissue samples

At the end of the experiment, animals were subjected to overnight fasting and blood was collected from the retro-orbital sinus. Serum was separated from the coagulated blood by centrifugation at 3000 r.p.m for 20 min and stored at 4˚C in a refrigerator for subsequent biochemical analyses. The animals were sacrificed with high dose ether and kidney specimens were removed, weighed and suspended in 10 percent buffered formalin to be processed for histopathological examination.

Chemicals and reagents

All chemicals and reagents were of analytical grade. Paracetamol was purchased from Getwell Pharmaceuticals Haryana, India. Silymarin tablets were bought from Micro labs limited, Mamring, South Sikkim, India. The biochemical estimation kits were bought from Avantor Performance Materials India Limited.

Biochemical analysis

Serum creatinine, urea, albumin levels were measured using commercial available kits following standard procedures (Jaffe MZ, 1886; Berthelot MP, 1859; Kaplan A, 1983).

Statistical analyses

Data were analyzed using one-way analysis of variance(ANOVA) followed by Dunnett's t-test using SPSS version 21. P value < 0.05 was considered significant.

RESULTS

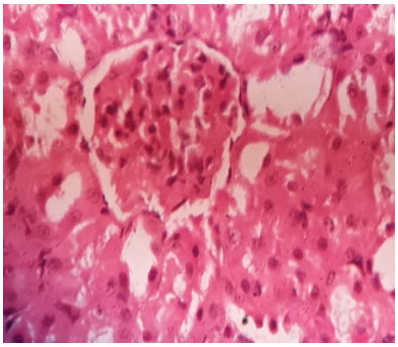
Table 1 Serum levels of urea, creatinine and albumin in the different treatment groups

Groups	Serum urea(mg/dl)	Creatinine(mg/dl)	Albumin(g/dl)
I	32.5±3.8	0.5±0.05	3.9±0.18
II	65.8±2.2**	2.6±0.35**	1.4±0.09**
III	34.3± 0.92††	0.62±0.02††	3.4±0.16††
IV	45.5±1.3*††	1.1±0.06††	2.0±0.09**†
V	35.8±1.1†††‡	0.69±0.01††	3.3±0.08*†††‡‡

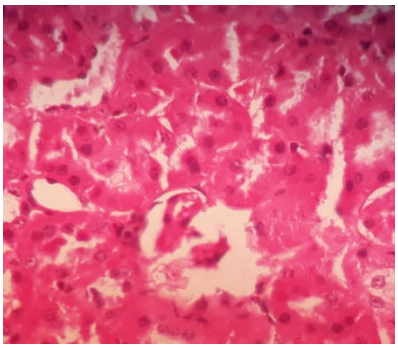
Values are expressed as mean ± SEM, Group I – normal control, Group II- PCM treated(2gm/kg), Group III - PCM 2mg/kg + silymarin(25mg/kg), Group IV- PCM 2mg/kg + MEEB(200mg/kg), Group V - PCM 2mg/kg + MEEB(400mg/kg); * P <0.05, ** P< 0.001 when compared with normal group; † P< 0.05, †† P< 0.001 when compared with toxic group; ‡ P<0.05 when compared with group IV Table shows the levels of serum urea, creatinine and albumin in the various treatment groups. PCM administration resulted in significant elevations in serum urea, creatinine and depletion in albumin levels (P<0.001) as compared to the healthy controls. However, pretreatment with MEEB significantly (P<0.05, P<0.001) prevented the biochemical changes.

Histopathological changes

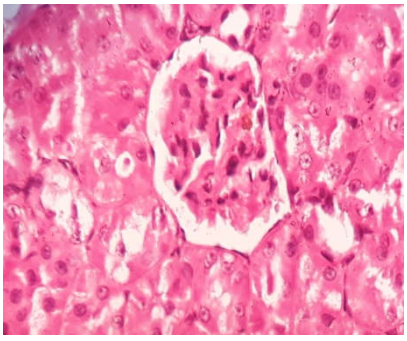
The histological features of the kidneys from various treatments groups are shown.



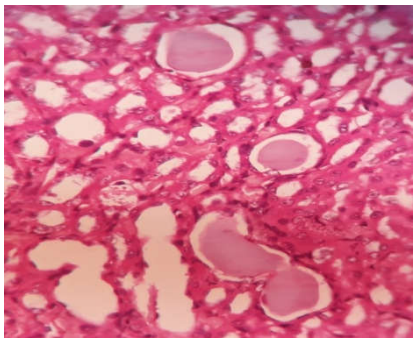
Normal control group



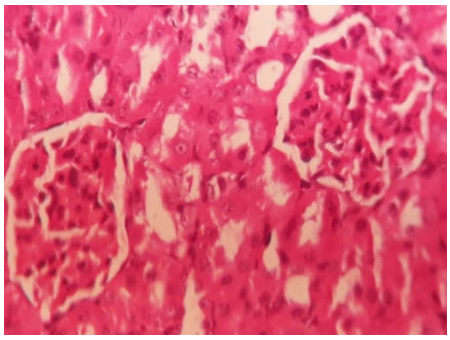
PCM 2g/kg treated group



Silymarin treated group



MEEB 200mg/kg treated group



MEEB 400 mg/kg treated group

Figure: Photomicrograph showing hematoxylin and eosin stained slides of kidney tissues from the various treatment groups (magnification 40X)

Kidneys from the control group had normal histologic morphology with intact glomeruli and tubules. Renal sections from PCM treated group showed glomerular atrophy, interstitial lymphocytic infiltration, tubular cast and necrosis. The silymarin treated group exhibited considerably mild changes. Stained sections of group treated with 200mg/kg showed some cast and necrosis while these were much reduced in the group treated with 400mg/kg of MEEB. These features were in line with the biochemical findings thus confirming the results.

DISCUSSION

Paracetamol toxicity can lead to severe morbidity and mortality. Potential mechanisms of renal toxicity based on both animal and human data include the cytochrome P-450 pathway, prostaglandin synthetase, and N-deacetylase enzymes (Bessems JG and Vermeulen NP, 2001). Paracetamol toxicity can cause acute tubular necrosis, which is one of the main causes of acute renal failure (Blantz RC, 1996).

Silymarin is a plant derived product and is known to have hepatoprotective effect. It has been found to have antioxidant and anti-inflammatory properties. Studies have also reported its protective role in diabetic nephropathy (Bahmani M *et al*, 2015).

The present study shows that rats treated with paracetamol 2g/kg developed nephrotoxicity as evidenced by the significant change in the levels of serum urea, creatinine and albumin when compared with the normal control group.

Creatinine is produced from creatine in the muscles and diffuses passively into the circulation and is subject to renal clearance (Waring WS and Moonie A, 2011). Urea is a major nitrogenous end product of protein and amino acid catabolism (Gowda S *et al*, 2011). Serum creatinine and urea concentrations are important biomarkers for detecting kidney injury. Hypoalbuminemia in renal failure is attributed to both a reduced synthesis and an increased degradation of albumin. Increased urinary excretion of albumin due to renal cell damage will also reduce its plasma level (Haller C, 2005). In our study, we found that pretreatment of the animals with MEEB could ameliorate these changes. Serum creatinine and urea levels were significantly reduced in test 1 and test 2 groups when compared with the group treated with PCM alone. Administration of the plant extract could significantly prevent the decline in serum albumin levels as well. Also it is seen that the plant extract at a dose of 400mg/kg could offer better protection. Histopathological examination also supported the biochemical results. These findings were in line with the previous similar studies (Ibrahim AA and Al-Shaikh TM, 2016). The protective effect of MEEB could be attributed to the presence of the phytoconstituents like flavonoids, tannins which are known to have antioxidant and radical scavenging properties (Khomdram SD and Singh PK, 2011) and will protect against the oxidative stress induced by nephrotoxic agents like paracetamol. Thus, the plant can be studied as a potential candidate for therapeutic use as a nephroprotective agent.

CONCLUSION

From the above observations we can conclude that the administration of methanolic extract of *Elsholtzia blanda* could protect from the nephrotoxic effects of high dose of paracetamol in albino rats. The biochemical and histopathological alterations were prevented by the pretreatment with this extract. However, further research need to be carried out to elucidate the clinical applications of this plant.

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