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Nephroprotective activity of *Pisonia aculeata* L. leaf extract against cisplatin induced nephrotoxicity and renal dysfunction in experimental rodents

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Pisonia aculeata L. (Nyctaginaceae), commonly called Devil's Claws or Pullback, is a folk medicinal plant of India. Herbal medicines due to lesser/no side effect, are being accepted by the society increasingly. Here, we investigated the protective effects of ethanol extract of *P. aculeata* leaves on cisplatin induced nephrotoxicity. Cisplatin (3 mg/kg, *i.p.*) co-administered to vehicle and extract (200, 400, 600 mg/kg)-fed rats every 5th day for 25 days. Serum level of urea, uric acid, creatinine, blood urea nitrogen, phospholipid and cholesterol increased, whereas urine urea, uric acid, creatinine, creatinine clearance rate was reduced in cisplatin control group. Cisplatin also negatively alters electrolyte balance, Na^+/K^+-ATPase activity and redox balance significantly. Treatment with extract for 21 days exerted beneficial effect and ameliorated urine and serum biochemical parameter to normal. Extracts induced a rise in Na^+/K^+-ATPase activity, and ameliorated level of different enzymatic and non-enzymatic antioxidants positively, whereas lipid peroxidation decreased significantly. Ethanol extract (400 and 600 mg/kg) ameliorated cisplatin-induced nephrotoxicity and other damaging effects caused by cisplatin evidenced by the change in its intrinsic biochemical/antioxidant properties. Taking into account these results, it can be assumed that *P. aculeata* leaves could be a future key candidate which may maximize the clinical use of cisplatin in the treatment of different cancer without nephrotoxicity.

Keywords: Antioxidant, Devil's Claws, Folk medicine, Herbal, Kidney disease, Serum biomarker

Drug induced nephrotoxicity is one of the major concerns in the present era due to increased such incidences with augmented use of modern medicines like anticancer drugs, non-steroidal anti-inflammatory drugs, antibiotics, etc[1]. Cisplatin is still widely prescribed for a diverse spectrum of cancer, despite its adverse effects like nephrotoxicity, bone marrow toxicity, neurotoxicity, ototoxicity, GIT toxicity, etc.[2-4]. Different investigations have confirmed that oxidative stress plays a key role in cisplatin induced nephrotoxicity[2,4].

Pisonia aculeata L. (Nyctagenaceae), commonly called Devil's Claws or Pullback, and locally *Ottu chedi*, is a thorny, large climbing shrub used by different ethnic people of India and other countries for the treatment of various diseases. Traditionally, leaves and bark of the plant are used to treat swelling, rheumatism and pulmonary complaints, in addition to its other medicinal value such as anti scabies, aphrodisiac and diuretic[5,6]. Antitubercular chromones and flavonoids were isolated from the plant root and stem[7]. The plant has been investigated for its significant hepatoprotective and antioxidant activity[8,9]. Our previous investigation reported anti-inflammatory, analgesic and antioxidant activity of *P. aculeata* leaves [9].

In the present study, we tried to evaluate the protective activity of the ethanolic extract of *Pisonia aculeata* leaves against cisplatin-induced nephrotoxicity.

Materials and Method

Collection and extraction of plant materials

Leaves of *Pisonia aculeata* were collected from Tirupathi, Andhra Pradesh, India and authenticated by Dr. Madhava Chetty, Department of Botany, SV University, Andhra Pradesh (Specimen No. 331). Leaves were dried in a shed and grind into a coarse powder. Dried powdered leaves (500 g) were extracted with ethanol using Soxhlet apparatus, and the solvent was evaporated to dryness to get solvent free extract[9]. The yield of the solvent free ethanol extract of *P. aculeata* leaves (PA-EE) was found to be 17.5% w/w.

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Experimental animals

Healthy Albino female mice (20-30 g, 24.83± 0.54 g) were used for acute toxicity study and Wistar rats (either sex) were used for the nephroprotective activity. Rodents were maintained under standard environmental conditions. The study was approved by the Institutional Animal Ethical Committee of Assam Downtown University (Approval No. AdtU/IAEC/ 2015/009). All animal experiments were carried out according to the guidelines of CPCSEA, Ministry of Environment and Forests, Government of India.

Acute toxicity study

Acute toxicity study was performed according to OECD guidelines No. 423 (Annexure 2d)[10]. Ethanol extract (PA-EE) were administrated orally (2000 mg/kg) in three mice. Presence or absence of any signs of toxicity or mortality was monitored.

Experimental design - Nephroprotective activity

Rats were housed in a temperature and humidity controlled animal house with a constant 12 h light/dark cycle with standard rat chow and water *ad libitum*. Animals were randomly divided into 5 groups, each consisting of six rats. Group I (control) and II (cisplatin control) received vehicle daily for 21 days. Animals were in Group III-V received ethanol extract (PA-EE) orally at a dose of 200, 400 and 600 mg/kg, respectively. Cisplatin (CP, 3 mg/kg body wt./day, *i.p*), in 0.9% saline injected every fifth day for 25 days (total four injections) to induce nephrotoxicity to the rats of Groups II-V [designated as CP-Control, PA-EE (200 mg/kg), PA-EE (400 mg/kg) and PA-EE (600 mg/kg)]. Normal saline in equivalent volume was given to the animals of Group 1 (control). The animals were sacrificed on the 25th day (5 days after the last injection of cisplatin) under light ether anesthesia[2,11].

Twenty four hours urine samples were collected on 25th day using metabolic cages. Under light anaesthesia blood samples were collected, and the serum was separated by centrifugation at 1000 ×*g* for 20 min. Different biochemical parameters were estimated using urine and serum sample. Kidney of each rat was removed after the animals were sacrificed and washed with ice-cold normal saline. Homogenates (10% w/v) were prepared with 0.1 M Tris–HCl buffer (pH 7.5) by centrifugation at 3000 ×*g* for 15 min, which was used to determine Na+/K+-ATPase activity and *in vivo* antioxidant activity.

Estimation of urea, uric acid, creatinine and creatinine clearance

Serum and urine were analyzed spectrophotometrically to determine levels of urea, uric acid and creatinine using commercially available diagnostic kits. Creatinine clearance as an index of glomerular filtration rate, which was estimated using the following equation[12]:

Creatinine clearance (mL/min)

$$= \frac{[\text{urinary Cr } (\text{mg/dL}) \times 24 \text{ h urine volume} (\text{mL})]}{[\text{serum Cr } (\text{mg/dL} \times 24 \times 60 \ (\text{min})]}$$

Estimation of blood urea nitrogen (BUN), phospholipid, and cholesterol

Serum phospholipids content was determined using a standard method[2]. Blood urea nitrogen (BUN) and serum cholesterol level were estimated by commercially available kits (Agapee Diagnostics, India).

Estimation of Na, K and Na+/K+–ATPase activity

Plasma potassium and sodium level was estimated by the colorimetric method and expressed as micromoles per litre of plasma. Flame spectrophotometer was used to estimate concentrations of Na^+ and K^+ ions in urine. Na^+/K^+-ATPase, is a membrane-bound enzyme and Na^+/K^+-ATPase activity was assayed by determining the quantity of phosphorous liberated from the incubation mixture containing tissue homogenate, ATP and the respective chloride salt of the electrolytes[13,14].

Estimation of enzymatic antioxidants

Superoxide dismutase (SOD) activity was measured by determining the inhibition of the generation of autocatalyzed adrenochrome in the presence of tissue homogenate. Catalase (CAT) activity was estimated by measuring the decomposition of H_2O_2 in the presence of catalase at 254 nm. The activity of glutathione reductase (GR) was estimated by a method that involves oxidation of NADPH into $NADP^+$ in the presence of oxidized glutathione. Glutathione peroxidase (GPx) activity was measured by monitoring the oxidation of reduced NADPH at 340 nm. Reduced glutathione (GSH) was determined by the spectrophotometric method of Asokkumar et al. Total melondialdehyde (MDA) was estimated as index of the degree of lipid peroxidation in kidney tissue[15].

Statistical analysis

The results are expressed as mean±S.E.M (n=6). Statistical difference was tested by using one-way analysis of variance followed by Tukey tests. A level of P <0.05 was used as the criterion for statistical

Table 1 — Effect of ethanol extract *Pisonia aculeata* leaves on serum and urine parameters of nephrptoxic animals

Group	Serum urea (mg/dL)	Serum uric acid (mg/dL)	Serum creatinine (mg/dL)	Urine urea (mg/dL)	Urine uric acid (mg/dL)	Urine creatinine (mg/dL)	Urine Volume (mL/24 h)	Creatinine Clearance (mL/min)
Control	35.31±2.21	1.22±0.20	0.82±0.05	137.60±6.61	6.70±1.33	42.12±2.44	13.44±1.46	0.479±0.11
CP-Control	69.91±4.44[c]	2.52±0.30[c]	1.45±0.12[c]	102.20±3.60[b]	4.12±0.62[c]	28.23±1.90[c]	9.04±1.03[b]	0.122±0.09[c]
PA-EE (200 mg/kg)	62.04±4.12 [↓11.3]	2.23±0.20 [↓11.5]	1.24±0.09[a] [↓14.5]	111.80±7.33[a] [↑8.6]	4.52±1.08 [↑9.7]	30.45±2.12 [↑7.9]	9.70±1.11 [↑7.3]	0.165±0.08
PA-EE (400 mg/kg)	45.99±2.91[b] [↓34.2]	1.49±0.27[b] [↓40.9]	1.02±0.09[b] [↓29.7]	126.72±6.80[c] [↑24.0]	6.01±1.25[c] [↑45.9]	38.71±2.32[b] [↑37.1]	10.80±1.92[b] [↑19.5]	0.285±0.10[c]
PA-EE (600 mg/kg)	37.70±2.79[c] [↓46.1]	1.32±0.20[c] [↓47.6]	0.91±0.10[c] [↓37.2]	132.37±6.01[c] [↑29.5]	6.59±0.81[c] [↑60.0]	40.03±2.32[c] [↑41.8]	12.99±1.17 [↑43.7]	0.397±0.11[c]

[Values are expressed as mean±SEM (n=6). CP, cisplatin; PA-EE, ethanol extract *P. aculeata* leaves. [a]P <0.05, [b]P <0.01, [c]P <0.01 when extract treated groups compared with diseases control (CP-control) group, and CP-control compared with healthy control group (ANOVA followed by the Tukey test). Values in parentheses represent percent change from control/disease control]

significance. Percentage increase or decrease in the value after extract treatment was also calculated that represent the percent change in value from control/disease control (this value was calculated by taking the mean value of control/disease control group and treatment group).

Results

Acute toxicity study

Common side effects such as mild diarrhea, loss of weight and depression of extract treated animals were recorded within the 7 days of observation. PA-EE did not produce any mortality or toxicity when tested through acute toxicity study.

Effect of extracts on urea, uric acid, creatinine and creatinine clearance

Effect of PA-EE on serum and urine level of urea, uric acid and creatinine were tabulated in Table 1. Repeated dose of cisplatin administration induced nephrotoxicity in rats evident by the marked rise in serum urea, serum uric acid, serum creatinine level, and significant reduction in urine urea, uric acid and creatinine level in the cisplatin control group. Treatment with PA-EE (600 mg/kg) cause significant reduction in serum urea (–46.1%), serum uric acid (–47.6%), serum creatinine (–37.2%) level, and increase in urine urea (+29.5%), urine uric acid (+60.0%), urine creatinine level (+41.8%) in spite of cisplatin administration. Results showed that PA-EE (400 mg/kg) produced a significant protective effect on cisplatin-induced nephrotoxicity. Cisplatin found to reduced creatinine clearance rate when compared to the control group, which was significantly increased further after treatment PA-EE (400 and 600 mg/kg).

Table 2 — Effect of ethanol extract *Pisonia aculeata* leaves on BUN, phospholipid, and cholesterol level

Group	BUN (mg/dL)	Phospholipid (mg/dL)	Cholesterol (mg/dL)
Control	13.20±2.41	97.52±5.16	115.32±6.07
CP-Control	37.90±3.66[c]	138.30±9.12[c]	156.02±6.39[c]
PA-EE (200 mg/kg)	33.98±3.31 [↓10.3]	129.70±8.99 [↓6.21]	147.22±7.02 [↓5.6]
PA-EE (400 mg/kg)	28.40±1.99[b] [↓25.1]	116.77±8.06[a] [↓15.6]	132.77±6.62[a] [↓14.9]
PA-EE (600 mg/kg)	20.22±2.55[c] [↓46.6]	107.83±7.55[b] [↓22.0]	124.32±7.13[c] [↓20.3]

[Values are expressed as mean±SEM (n=6). CP, cisplatin; PA-EE, ethanol extract *P. aculeata* leaves. [a]P <0.05, [b]P <0.01, [c]P <0.01 when extract treated groups compared with diseases control (CP-control) group, and CP-control compared with healthy control group (ANOVA followed by the Tukey test). Values in parentheses represent percent change from control/disease control]

Effect of PA-EE on BUN, phospholipid, and cholesterol level

Administration of cisplatin to healthy rats caused a significant increase in BUN, serum phospholipid and cholesterol level. Treatment with PA-EE (400 and 600 mg/kg) significantly prevents such alteration and reduced BUN, serum phospholipid and cholesterol level compare to nephrotoxic group. PA-EE (600 mg/kg) administration resulted in 46.6% increase in BUN; 22.0% and 20.3% reduction in phospholipid content and cholesterol level when compared with nephrotoxic group (Table 2).

Effect of extracts on Na, K level and Na–K–ATPase activity

A small insignificant decrease in serum sodium level and a significant reduction in serum potassium level were observed in CP-control group. PA-EE (600 mg/kg) administration enhances serum sodium (7.1%) and serum potassium level (58.2%). PA-EE (400 and 600 mg/kg) also reduced the excretion of urinary Na^+ (35.4%) and K^+ (56.6%) significantly (Table 3).

The activities of Na^+/K^+-ATPase significantly (P<0.05) decreased in the kidney tissue after cisplatin treatment compared to normal controls. Administration of PA-EE (400 and 600 mg/kg) along with cisplatin significantly (P <0.05) prevented the decrease in the activities of Na^+/K^+-ATPase in intoxicated rats (Fig. 1).

Effect of PA-EE on enzymatic and non-enzymatic antioxidants

The effect of PA-EE was estimated on the level of various enzymatic and non-enzymatic antioxidants when administered in nephrotoxic animals (Table 4). Level of SOD, CAT, GPx, GR, GSH significantly decreased after cisplatin induction, whereas the level of MDA increases. Cisplatin-induced reduction in the level of endogenous antioxidants was inhibited significantly after administration of the extract. PA-EE at a dose of 400 and 600 mg/kg produced significant protective effect and prevented the oxidative stress in kidney tissue as evident by the increased level of antioxidants after treatment with PA-EE. After receiving the PA-EE in nephrotoxic animals the level of MDA reduced by 68.1 and 62.3% (63% by DIME, −54% by DIEE, −25% by DIPE) compare to CP-control group (Table 4).

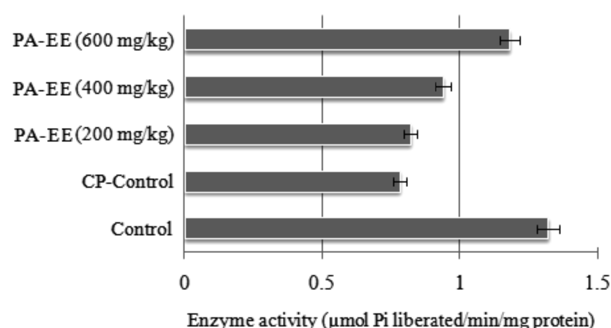

Fig.1 — Effects of ethanol extract *Pisonia aculeata* leaves on Na^+/K^+-ATPase activity. Values are expressed as mean±SEM (n=6). CP, cisplatin; PA-EE, ethanol extract *P. aculeata* leaves

Discussion

The relation between oxidative stress and nephrotoxicity was well established. It was also well documented that inflammation, oxidative stress is playing a key role in cisplatin induced nephrotoxicity[1,3.] Previous investigations showed that leaves of *P. aculeata* exhibited strong anti-inflammatory and antioxidant activity[9]. Therefore, this investigation carried out to find the protective effect of PA-EE against cisplatin-induced nephrotoxicity. A number of studies were conducted to evaluate the nephroprotective activity of traditional medicinal plants, isolated phytochemicals. Protective activity of green tea against nephrotoxicity induced by multiple-dose cisplatin was evaluated[11].

Table 3 — Effect of ethanol extract *Pisonia aculeata* leaves on sodium and potassium level

Group	Serum Na^+ (mmoL/L)	Serum K^+ (mmoL/L)	Urinary Na^+ excretion (µmoL/24 h)	Urinary K^+ excretion (µmoL/24 h)
Control	134.20±4.20	6.32±1.12	120.52±5.90	259.63±14.91
CP-Control	128.10±2.31[b]	3.80±0.93[b]	201.08±7.02[c]	458.82±14.44[c]
PA-EE (200 mg/kg)	130.13±3.39 [↑1.6]	4.02±1.02 [↑5.8]	189.20±6.22[a] [↓5.9]	429.05±14.91 [↓6.5])
PA-EE (400 mg/kg)	135.54±3.30 [↑5.8]	5.12±1.25[c] [↑34.7]	144.01±6.29[a] [↓28.4]	335.33±12.04[c] [↓26.9])
PA-EE (600 mg/kg)	137.17±3.87[a] [↑7.1]	6.01±0.20[b] [↑58.2]	129.88±6.09[a] [↓35.4]	288.50±15.06[c] [↓56.6]

[Values are expressed as mean±SEM (n=6). CP, cisplatin; PA-EE, ethanol extract *P. aculeata* leaves. [a]P <0.05, [b]P <0.01, [c]P <0.01 when extract treated groups compared with diseases control (CP-control) group, and CP-control compared with healthy control group (ANOVA followed by the Tukey test). Values in parentheses represent percent change from control/disease control]

Table 4 — Effect of ethanol extract *Pisonia aculeata* leaves on enzymatic and non-enzymatic antioxidant level

Group	SOD (µmol/min/mg protein)	CAT (µmol/min/mg protein)	GPx (µmol/min/mg protein)	GR (µmol/min/mg protein)	GSH (µM GSH/g tissue)	MDA (nM/ min/mg protein)
Control	4.02±0.75	29.03±2.98	20.33±1.82	1.30±0.38	12.22±2.13	1.04±0.24
CP-Control	2.81±0.75[c]	21.34±2.72[c]	11.14±1.06[c]	0.60±0.27[c]	6.77±1.84[c]	3.98±0.47[c]
PA-EE (200 mg/kg)	3.11±0.94 [↑10.7]	22.88±2.55 [↑7.2]	13.39±1.68 [↑20.2]	0.71±0.38[a] [↑18.3]	8.02±2.31 [↑18.5]	3.46±0.59 [↓13.1]
PA-EE (400 mg/kg)	3.98±0.84[c] [↑41.6]	25.68±2.23[b] [↑20.3]	17.33±1.90[c] [↑55.6]	1.09±0.19[c] [↑81.7]	9.99±2.03[c] [↑47.6]	1.50±0.64[c] [↓62.3]
PA-EE (600 mg/kg)	4.12±0.72[c] [↑46.6]	28.75±2.33[b] [↑34.7]	19.37±1.83[c] [↑73.87]	1.25±0.28[c] [↑108.3]	11.54±1.80[c] [↑70.5]	1.27±0.23[c] [↓68.1]

[Values are expressed as mean±SEM (n=6). CP, cisplatin; PA-EE, ethanol extract *P. aculeata* leaves. [a]P <0.05, [b]P <0.01, [c]P <0.01 when extract treated groups compared with diseases control (CP-control) group, and CP-control compared with healthy control group (ANOVA followed by the Tukey test). Values in parentheses represent percent change from control/disease control]

Administration of green tea resulted in the reversal of cisplatin-induced alterations. Activities of the carbohydrate metabolism enzymes, enzymes of brush border membrane, and 32Pi transport increased after green tea administration. Green tea (3 mg/kg body wt./day for 25 day) ameliorated cisplatin-induced deleterious effects and enhanced enzymatic/non-enzymatic antioxidant level. Our study also produced a similar effect. The beneficial effect of essential oil of fennel was examined on cisplatin-induced nephrotoxicity in ovariectomized rats. Trans-anethole is the major composition of fennel essential oil. Fennel essential oil failed to exhibit protective against nephrotoxicity. It was also reported that fennel essential oil is a source of phytoestrogen and it did not cause kidney damage. This essential oil exhibited a similar effect like estrogen was not a nephroprotectant agent in that study[16]. A study found that *Dillenia indica* fruit (methanol and ethyl acetate extracts) exhibited a protective effect against multiple doses of cisplatin induced nephrotoxicity. After 25 days treatment with extract serum biochemical and urine parameter ameliorated positively. Extract found to enhance Na^+/K^+-ATPase activity, endogenous antioxidants activity, whereas lipid peroxidation reduced significantly[2]. Another study investigated effect of *Nigella sativa* extract alone and in combination with vitamin E against cisplatin-induced nephrotoxicity. Extract and vitamin E produced significant improvement in tissue damage caused by cisplatin. Serum and tissue total thiol content also improved in extract-treated group[17]. In our study also *Pisonia aculeata* L. leaf extract produced a significant protective effect when administered for 25 days along with cisplatin. It showed significant change in the biochemical parameters and also exhibited antioxidant activity. The effect of extract is comparable to that of other plants i.e., *Nigella sativa*[18,19], *Dillenia indica*[20,21], and green tea[22,23] investigated as discussed.

Urea is a nitrogen-containing metabolic product generated during protein metabolism. End-product generated from an exogenous pool of purines and endogenous purine metabolism is uric acid[24,25], whereas creatinine is a generated as a breakdown product of creatine phosphate in muscle, and considered as an indicator of kidney function[2,26]. Serum urea, creatinine and uric acid may cause modification of the glomerular filtration rate (GRF) and rise in their serum levels are related to renal damage. Parenchymal injury may responsible for an increased level of serum urea level. Hyperuricemia is considered as a renal prognostic factor, which may be related to the increased production of oxygen species as uric acid scavenges peroxynitrite[27,28]. Increased serum creatinine level is considered as the most reliable indicator of the first phase of any kidney disease[25]. Kidney is an important organ that works continuously to eliminate toxic substances. When cisplatin injected in repeated dose it was found to cause marked dysfunction of rat kidney as evident by increased serum urea, uric acid, creatinine level that are considered as diagnostic indicators of nephrotoxicity. Level of creatinine, urea, uric acid in urine and creatinine clearance also decreased significantly after cisplatin injection. This alteration may be occurred due to the decrease in the GFR or may be related to the oxidative stress that responsible for contraction of mesangial cells, modification of filtration surface area and change of the ultrafiltration coefficient factor[2,29]. In the present study, administration of PA-EE at a dose of 400 and 600 mg/kg positively ameliorated the serum and urine parameters. Creatinine clearance rate was also raised after extract administration. Results indicated the protective effect of PA-EE against cisplatin-induced nephrotoxicity.

Cisplatin is responsible for the destruction of proximal and distal tubules preceded the renal hemodynamics, decreased the reabsorption, increased vascular resistance, that in turn responsible for an increased level of BUN[2,29]. In the present study, PA-EE found to reduce the level of BUN near to normal. Significant (P <0.001) enhancement in the levels of serum phospholipids was documented in CP-control group, which is in line with earlier reported studies[2,11]. This change in serum phospholipids level may due to the cisplatin-induced damage of membrane phospholipids. PA-EE (400 and 600 mg/kg) cause a significant decrease in the serum phospholipid level and reduction in serum cholesterol level that may be considered as a healthy indicator.

Toxic agents, chemicals, infectious agents, certain drugs etc. can cause kidney that finally leads to electrolyte imbalance[28]. In the present study, level of serum sodium did not alter significantly after cisplatin treatment, though serum level of potassium reduced significantly (P <0.01) in nephrotoxic animal compare to normal rats. Hypokalemia is a usual electrolyte imbalance observed during cisplatin treatment which is linked to the enhanced renal reabsorption in response to

decreased intestinal absorption of potassium[2,28]. Urinary excretion of sodium and potassium enhanced significantly in nephrotoxic animals, which indicated the abnormality in kidney function. Results of the present study indicated the potentiality of PA-EE to overcome electrolyte imbalance. ATPases are the integral membrane proteins which require phospholipids and thiol groups to maintain their structure and function[2]. Cisplatin is responsible for the alteration of electrolytes homeostasis that decreased the activity of Na^+/K^+-ATPase and finally leading to cell death[2,24]. Result reviled that PA-EE treatment restored Na^+/K^+-ATPase activity.

Endogenous antioxidant system (enzymatic and non-enzymatic) are responsible for maintaining redox balance and to prevent oxidative stress[2]. Cisplatin found to decrease the level of SOD, CAT, GPx, GR and GSH significantly in this present study, which further proves the role of cisplatin-induced oxidative stress in nephrotoxicity. SOD is an endogenous antioxidant enzyme that scavenges superoxide radicals to less reactive H_2O_2 and O_2, while CAT scavenges H_2O_2 to water and molecular oxygen[2,30]. GPx play a key role in detoxification of H_2O_2 by inducing the oxidation of GSH. Oxidized glutathione, produced upon reduction of organic peroxide, was recycled to its reduced form by GR[15,31]. GSH is a non-enzymatic antioxidant that maintains cell integrity by preventing oxidative stress through the detoxification of reactive species. GSH also detoxifies the cisplatin through the generation of GSH adducts[2,15]. In this study, PA-EE effectively averted the depletion of SOD, CAT, GPx, GR and GSH. MDA is considered as a good indicator of the extent of lipid peroxidation. Enhanced accumulation of lipid peroxides in tissue can decrease antioxidant enzyme and GSH, which in turn responsible for renal toxicity[32]. PA-EE treatment caused decreased level of MDA in dose dependent manner. Therefore, our study confirms the potent antioxidant activity demonstrated by the PA-EE, as extracts positively ameliorate the level of enzymatic and non-enzymatic antioxidants to normal, and reduces lipid peroxidation. This ability of extracts may contribute to the nephroprotective activity of extracts.

Conclusion

In the light of biochemical results and antioxidant investigations, the present results confirmed that ethanol extract of *Pisonia aculeata* leaves confer a protective effect against cisplatin induced nephrotoxic and renal dysfunction. This protective effect of *P. aculeata* leaf extract, could be partly due to their antioxidant activity as the extract showed excellent effectiveness by averting the depletion of SOD, CAT, GPx, GR and GSH. Extract treatment also caused decreased level of MDA in dose dependent manner. Taking into account these results, we assume that the detailed analysis of the plant leaves could be useful to maximize the clinical use of cisplatin in the treatment of different cancer without nephrotoxicity and also found effective to manage oxidative stress.

Conflict of Interest

The authors declare no conflict of interests.

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