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Nephroprotective effect of ethanolic extract of *Pedalium murex* in cisplatin induced nephrotoxicity in wistar rats

Santosh Tambade and Sushma Ghadigaonkar

Abstract
Chemotherapy and radiotherapy are the most common modalities of cancer treatment. Cisplatin (Cis-diamminodichloro platinum II) is currently one of the most important chemotherapeutic drugs used in treatment of a wide range of solid tumors – head, neck, ovarian and lung cancers. However the clinical usefulness of Cisplatin is limited by its cumulative nephrotoxicity and neurotoxicity. Thirty six Wistar rats of either sex were randomly selected and divided into six groups Group A served as control, Group B served as positive control (single dose of Cisplatin @ 7.5 mg/kg of body weight I/P) and rats of Group C were treated with single dose of Cisplatin @ 7.5 mg/kg of body weight and preventive dose of *P. murex* Linn. fruit extract (500 mg/kg P.O.). Group D comprised of single dose of @ 7.5 mg/kg of body weight and curative regimen of P. *murex* Linn. Fruit extract (1000 mg/kg of body weight, P.O.) from 8th to 14th day. Rats of Group E given single dose of Cisplatin @ 7.5 mg/kg of body weight and Taurine (1000 mg/kg of body weight, P.O.) and Group F served as vehicle control (0.125% tween 80 w/v). The Cisplatin treated rats showed significant reduction in body weight, Hb, TEC, TLC and PCV While; they had showed significant increase in relative kidney weights, BUN, creatinine and uric acid levels. However, rats treated with preventive regimen of *P. murex* Linn extract revealed significant increase in body weight, Hb, TEC, TLC and PCV levels while significantly decreased relative kidney weights, BUN, creatinine and uric acid levels were noticed than the curative dose of the same. The histopathological observation of kidney in Cisplatin alone treated rats at the both interval showed moderate to marked tubular damage with degeneration and necrosis of tubular epithelium.
The mechanism involved in exhibiting nephroprotective activity might be due to antioxidant activity of phytoconstituents of *P. murex* Linn. Fruit extract which may act as free radical scavengers that restored the Cisplatin induced oxidative stress in animals.

Keywords: *Pedalium murex*, gokharu, cisplatin, nephrotoxicity, wistar rats, taurine

Introduction
Nephrotoxicity is one of the most common kidney problems and occurs when body is exposed to a drug or toxin. Drug induced nephrotoxicity is an important cause of renal failure. Chemotherapy and radiotherapy are the most common modalities of cancer treatment. Cisplatin (Cis-diamminodichloro platinum II) is currently one of the most important chemotherapeutic drugs used in treatment of a wide range of solid tumors-head, neck, ovarian and lung cancers. However the clinical usefulness of Cisplatin is limited by its cumulative nephrotoxicity and neurotoxicity. In the present study the ethanolic extract of *P. murex* was studied for nephroprotective activity in Wistar rats. The nephroprotective activity was studied in cisplatin induced nephrotoxicity using Taurine as standard which showed significant nephroprotection. Preventive dose of *P. Murex* extract provided significant protection and improvement against cisplatin induced nephrotoxicity than Taurine.
Cisplatin is currently most important chemotherapeutic drug used in treatment of wide variety of head, neck, ovarian & lung cancers. The most serious cumulative adverse effect of Cisplatin is nephrotoxicity & neurotoxicity (Joy & Nair 2008) [1]. Nephrotoxicity caused by Cisplatin probably due to apoptosis, inflammatory mechanism & generation of reactive oxygen species (Dirk TH *et. al*, 1985) [2]. Hence systematic pharmacological evaluation of nephroprotective effect of ethanolic extract of fruit of *Pedalium murex* Linn against experimentally induced renal damage. A variety of chemicals have been isolated & characterized from plant *Pedalium murex* Linn. They are classified under flavonoids, Tri-terpenoids, lipids, steroid acids, carbohydrate & amino acids. The juice of fruit is believed to dissolve the kidney stone (Kirtikar & Basu 1933, Rastogi & Malhotra 1991) (Satyavati & Gupta 1987) [3].

The present investigation was undertaken to evaluate the effect of ethanolic fruit extract of *Pedalium murex* Linn. Plant

Materials and Methods

Preparation of extract

The ethanolic extract of fruit of *Pedalium murex* Linn was prepared by using Soxhlet extraction apparatus. The 25gm powders were placed in thimble made up of thick filter paper which was loaded into the main chamber of the apparatus. Ethanol was then poured to complete one cycle & it was again added to dip the thimble half a length. The solvent (ethanol) was heated at 50c till clear solvent visible to main chamber of the apparatus. After extraction, the contents of receiver flask were subsequently transferred to sterilized evaporating bowels, already weighed & placed under fan for evaporation of the solvent. The residue left in the bowels once again weighed to known amount of extract & extractability percentage.

Phytochemical composition: The ethanolic fruit extract of *Pedalium murex* Linn was subjected to series of phytochemical tests (Prabhuji *et al.* 2005) [4] to determine the presence of alkaloids, glycosides, tannins, resins, steroids, saponins& flavonoids. Alkaloids were measured by Dragendorff's reagent test & Mayer's test. Glycosides were measured by Benedicts test. Saponins were measured by foam test. Flavonoids were measured by ferric chloride test & Shinoda test.

Experimental animals

Forty eight wistar rat of either sex, weighing 200-250g were used for this study. The animals were divided into four groups of twelve animals each. The experimental protocol was approved by Institutional Animal Ethics committee (IAEC).The rats were house in clean poly propylene cages, under controlled environmental conditions ($25+2^0$c) & 12 hour dark & light cycles. The animals were provided clean, autoclaved, dried rice husk as bedding material which was changed on alternate days. The rats were maintained on standard balanced diet with free access to clean deionized drinking water ad libitum throughout the experimental period.

Clinical symptoms and behavioral studies

The rats under experimentation were observed. Thrice daily (morning, afternoon & evening) for clinical signs & behavior changes till the end of the experiment.

Physical parameters

Body weights were recorded at weekly intervals till the day of sacrifice.

Haematobiochemical assay

The blood samples were collected from retro-orbital plexus of rat in sterile EDTA vials & were analyzed for evaluation of haematogical parameters *viz*.; hemoglobin (Hb) concentration, total erythrocyte count (TEC), total leucocytes count (TLC) & packed cell volume (PCV) as per the method described by Benjamin. The blood samples were processed for separation of serum & the concentration of serum biochemical parameters *viz*. Serum alanine transaminase (ALT), Serum Aspartate transaminase (AST), Blood urea nitrogen (BUN) & serum creatinine (sc) were assessed by serum biochemistry semi-auto analyzer (Erba-chem7) employing biochemical's kits manufactured by Transasia Ltd. Mumbai for the determination of BUN by Urease method, ALT & AST by IFCC method & serum creatinine by Jaffe's method.

Statistical analysis: The data were statistically analyzed using WASP 2 computer software.

Result and Discussion

The investigation included phytochemical studies, clinical studies, behavioral changes, body weight changes &hematological& biochemical parameters. The ethanolic extract of fruit of *P. murex* Linn was made and 4.8g of extract was obtained from 25g *P. murex* Linn fruits. The percent extractability was found to be 19.2 per cent. Result of study were similar to findings of Nalini *et al*. (2011) also observed 14.5% methanol extractability of *P. murex* Linn and revealed presence of flavonoids, alkaloids, glycosides, steroids, phenols, and Terpenoids. It was observed that group II (positive control) animals with induced Cisplatin toxicity showed varying degrees of clinical signs including lethargy, loss of appetite, weight loss, loss of hair, nausea. The body weight (g) of group B rats on from 0 to 7 day (148+12.32) was significantly lower ($p<0.05$) than the 7 day body weight (222+ 16.55) of the rats in control Group. Decline in body weight is a feature of Cisplatin induced nephrotoxicity in rats & confirmed to the findings of Gaedeke *et al.* (1996) [7] & Devi (1999). The body weights of group III (standard treatment) rats which were administered Taurine with Cisplatin.

Hemoglobin, total erythrocyte count (TEC) & total leucocytes count (TLC) of group B rats positive control showed significant reduction as compared to control rats (Group A) due to nephrotoxicity, while group C rats treated with PMEFE treatment with Cisplatin showed significant rise in all these parameters than group B rats and was not different from group D rats treated with Taurine indicating that PMEFE was as effective as the standard drug Taurine in protecting haematic system during Cisplatin nephrotoxicity.

There was significant ($p\leq0.05$) rise in the levels of Serum Alanine Transaminase (ALT), Serum Aspartate Transaminase (AST) & Serum Creatinine in group B rats treated with Cisplatin compound to control however more significant reduction in mean BUN values was observed in rats treated with PMEFE when compared to Taurine. The present study were similar to the findings of Sreedevi *et al.*, (2011) [11] who reported that co-administrate of either ethanolic &Aqueous extract of *P. murex* @ 600mg/kg body weight with Cisplatin significantly reduced AST, BUN & Serum Creatinine. There was significant improvement in all these parameters group C (test treatment) & group D (standard treatment) rats over the group B (positive control) rats indicating the ameliorative effect of the medications. The levels of AST & ALT in group c (test treatment) rats was significantly ($p< 0.05$) lower than group D (standard treatment) rats indicating better nephroprotective action of *Pedalium murex* than Taurine.

Cisplatin toxicity is a sequel to production of free radicals. The mechanism involved in exhibiting nephroprotective activity might be due to antioxidant activity of phytoconstituents of *P. murex* Linn fruit extract which may act as free radical scavenger that restored the Cisplatin induced oxidative stress in animals. Taurine confers nephroprotection as it is an endogenous antioxidant (Mina *et al.* 2011) [6].

Table 1: Effect of preventive regimen of *Pedalium murex* L. fruit extract on Blood Urea Nitrogen (mg/dl) in cisplatin induced nephrotoxic rats

Group	Treatments	BUN (mg/dl) (mean ± SE)		
		0 Day	7 Day	14 Day
A	Control	17.00±0.00	15.78 ±0.08	16.32± 0.09
B	Cisplatin @ 7.5 mg/kg body wt. i.p.	18.02^{b} ±0.13	85.00^{a}**± 0.00	78.10^{a}**± 0.48
C	Cisplatin @ 7.5 mg/kg body wt. i.p. + *P. murex* L. fruit extract @ 500 mg/kg body wt. p. o.	18.35^{b} ±0.09	32.78^{c}**±0.07	26.47^{c}**± 0.11
D	Cisplatin @ 7.5 mg/kg body wt. i.p. + Taurine @ 1000 mg/kg body wt. p.o.	17.48^{c} ±0.12	39.00^{b}**±0.00	28.15^{b}**± 0.06
E	Vehicle control	19.00±0.28	17.34±0.15	19.15± 0.04

Means bearing different superscripts within the same column differ significantly (P<0.05)
* = Significantly different at 5% level (P≤0.05) as per 't' test
** = Significantly different at 1% level (P≤0.01) as per 't' test

Table 2: Effect of curative regimen of *Pedalium murex* L. fruit extract on Blood Urea Nitrogen (mg/dl) in cisplatin induced nephrotoxic rats

Group	Treatments	BUN (mg/dl) (Mean ± SE)		
		Day 0	Day 7	Day 14
A	Control	17.00±0.00	15.78 ±0.08	16.32 ± 0.09
B	Cisplatin @ 7.5mg/kg body wt. i.p.	18.02^{b} ±0.13	85.00^{a}**±0.00	78.10^{a}**± 0.48
D	Cisplatin @ 7.5mg/kg body wt. i/p + *P. murex* L. fruit extract @ 1000 mg/kg body wt. p.o.	19.00^{a} ± 0.28	83.29^{b}**± 0.16	38.99^{b}**± 0.23

Means bearing different superscripts within the same column differ significantly (P<0.05)
* = Significantly different at 5% level (P≤0.05) as per 't' test
** = Significantly different at 1% level (P≤0.01) as per 't' test

Table 3: Effect of preventive regimen of *Pedalium murex* L. fruit extract on Creatinine (mg/dl) in cisplatin induced nephrotoxic rats

Group	Treatments	Creatinine (mg/dl) (mean ± SE)		
		0 Day	7 Day	14 Day
A	Control	0.52 ±0.01	0.60 ±0.00	0.58 ± 0.00
B	Cisplatin @ 7.5 mg/kg body wt. i.p.	0.49^{c} ±0.01	3.90^{a}±0.02	3.79^{a}± 0.05
C	Cisplatin @ 7.5 mg/kg body wt. i.p. + *P. murex L.* fruit extract @ 500 mg/kg body wt. p.o.	0.54^{b} ±0.01	1.42^{c}**±0.06	0.97^{c}**± 0.00
E	Cisplatin @ 7.5 mg/kg body wt. i.p. + Taurine @ 1000 mg/kg body wt. p.o.	0.61^{a} ±0.02	1.69^{b}**±0.00	1.21^{b}**± 0.06
F	Vehicle control	0.54±0.01	0.48±0.02	0.60 ± 0.01

Means bearing different superscripts within the same column differ significantly (P<0.05)
* = Significantly different at 5% level (P≤0.05) as per 't' test
** = Significantly different at 1% level (P≤0.01) as per 't' test

Table 4: Effect of curative regimen of *Pedalium murex* L.fruit extract on Creatinine (mg/dl) in Cisplatin induced nephrotoxic rats

Group	Treatments	Creatinine (mg/dl) (Mean ± SE)		
		Day 0	Day 7	Day 14
A	Control	0.52±0.01	0.60 ±0.00	0.58 ± 0.00
B	Cisplatin @ 7.5 mg/kg body wt. i.p.	0.49^{b} ±0.01	3.90^{a}±0.02	3.79^{a} ± 0.05
D	Cisplatin @ 7.5 mg/kg body wt. i.p. + *P. murex* L. fruit extract @ 1000 mg/kg body wt. p. o.	0.62^{a} ±0.02	3.52^{b}**± 0.02	2.07^{b}**± 0.03

Means bearing different superscripts within the same column differ significantly (P<0.05)
* = Significantly different at 5% level (P≤0.05) as per 't' test
** = Significantly different at 1% level (P≤0.01) as per 't' test

Table 5: Effect of preventive regimen of *Pedalium murex* L. fruit extract on haemoglobin (g/dl) in cisplatin induced nephrotoxic rats

Group	Treatments	Haemoglobin(g/dl) (mean ± SE)		
		0 Day	7 Day	14 Day
A	Control	11.74 ± 0.11	11.92± 0.12	11.83± 0.15
B	Cisplatin @ 7.5 mg/kg body wt. i.p.	12.25^{ab} ± 0.14	9.30^{a} ± 0.15	9.50^{a} ± 0.11
C	Cisplatin @ 7.5 mg/kg body wt. i.p. + *P. murex* L. fruit extract @ 500 mg/kg body wt. p. o.	11.95^{ab} ± 0.29	10.97^{c}± 0.21	11.34^{b} ± 0.18
E	Cisplatin @ 7.5 mg/kg body wt. i.p. + Taurine @ 1000 mg/kg body wt. p.o.	12.1^{a} ± 0.11	10.59^{c} ± 0.18	11.10^{d} ± 0.17
F	Vehicle control	12.23± 0.34	12.00± 0.24	11.95± 0.15

Means bearing different superscripts within the same column differ significantly (P<0.05)
* = Significantly different at 5% level (P≤0.05) as per 't' test
** = Significantly different at 1% level (P≤0.01) as per 't' test

Table 6: Effect of curative regimen of *Pedalium murex* L.fruit extract on haemoglobin (g/dl) in cisplatin induced nephrotoxic rats

Group	Treatments	Haemoglobin(g/dl) (Mean ± SE)		
		Day 0	Day 7	Day 14
A	Control	11.74± 0.11	11.92± 0.12	11.83± 0.15
B	Cisplatin @ 7.5 mg/kg body wt. i.p.	12.25^{a} ± 0.14	9.30^{b} ± 0.15	9.50^{c} ± 0.11
D	Cisplatin @ 7.5 mg/kg body wt. i.p. + *P. murex* L.fruit extract @ 1000 mg/kg body wt. p.o.	12.02^{ab} ± 0.12	9.67^{b}*±0.20	10.8^{b}*± 0.45

Means bearing different superscripts within the same column differ significantly (P<0.05)
* = Significantly different at 5% level (P≤0.05) as per 't' test

Conclusion

This study revealed that Cisplatin induced nephrotoxicity could be prevented by administration of ethanolic fruit extract of *P. murex* L-@ 500mg/kg body weight per os along with Cisplatin in wistar rats.

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