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In-Vivo Study of Protective Role of *Moringa oleifera* Aqueous Pod Extract in Cisplatin Induced Nephrotoxicity

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Abstract

The present study investigates aqueous pod extract of *Moringa oleifera* for its protective role in cisplatin induced nephrotoxicity. The experiment was designed for 14 days and male wistar rats were used as experimental animal. Rats were divided into 7 groups (n = 6). Group 1 (normal control), group 2 (vehicle control), group 3 (cisplatin control) given cisplatin, 12 mg/kg Body Weight (BW) intraperitoneally in 0.9% saline on 11th day of treatment. Group 4 to 7 was given pod extracts *via* oral gavage in different doses 200 mg/kg and 400 mg/kg BW form day 1- 13, group 6 and 7 was also given cisplatin (12 mg/kg BW) on day 11. On 14th day blood sample were collected for serum analysis and all animals were sacrificed to study biochemical markers of renal dysfunction and histopathology study. Serum analysis of creatinine and blood urea nitrogen showed treatment with lower dose (i.e., 200mg/kg BW) significantly lowers the enhanced levels in cisplatin treated rats. Biochemical analysis showed lower dose significantly enhanced renal Catalase, SOD, and GPx activity while higher dose significantly enhances GPx and lowers renal MDA level in treated rats. The extract also improves histological damage. The study concluded that *M. oleifera* aqueous pod extract reduces renal damage caused by cisplatin treatment.

Keywords: Cisplatin, *M. oleifera, Moringaceae*, Nephrotoxicity, Oxidative Stress, Pod Extract

1. Introduction

Cisplatin (cis-diaminedichloroplatinum II) is a platinum containing antineoplastic drug, and since its approval *via* FDA in 1978, it is a widely used anticancer drug, used to treat many solid tumors mainly the testicular cancer with 90% cure rates, it is also widely used to treat head and neck, ovarian, cervical and small cell lung cancer[1,2]. However, its use in higher doses causes several side effects among which nephrotoxicity is the main adverse effect effecting approximately 30% of patients[3]. The major event among the pathways involved in cisplatin induced nephrotoxicity is oxidative stress. Cisplatin causes reduction in antioxidant status leading to depletion of enzymatic and non-enzymatic antioxidant defense[4–7]. Cisplatin is also associated with increase in lipid peroxidation leading to changes in membrane permeability[8,9]. Current measures of nephroprotection involve large amount of hydration and use of diuretics during treatment with cisplatin, however, these measures are not effective in eliminating toxic effects. Therefore, prevention of cisplatin toxic effects in renal tissue becomes important for the chemotherapeutic treatment.

M. oleifera belongs to family *Moringaceae* and commonly known as "drumstick tree". *M. oleifera* are richer source of Vitamins A, B, C, D and E and minerals like Calcium, Iron, Magnesium, Zinc and Manganese[10–12]. It has more than 40 natural antioxidants. *Moringa* is used as herbal medicine by Indians and Africans and it is known to cure more than 300 diseases. Moringa pods are used to treat diarrhea, liver, spleen problems and joint pain[13]. Abdulkadir *et al.*,[14] reported the antioxidative properties of plant parts

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of *M. oleifera*. A study reported the possible Chemo preventive potential of *M. oleifera* pods against chemical carcinogens *via* reducing oxidative stress[15]. A recent study showed the anti-nephrotoxic effect of *M.oleifera* pod against DMBA-induced renal carcinogenesis[16].

Based on the pharmacological effects and ethno botanical reports of *M. oleifera*, the present investigation was focused on the protective role of its aqueous pod extract in cisplatin induced nephrotoxicity by measuring enzymatic activities such as SOD, CAT and GPx along with the hematological and histopathological study.

2. Materials and Methods

2.1 Chemicals

Cisplatin was purchased from Thermo fisher, Waltham, USA. NBT (Nitroblue tetrazolium chloride), NADPH (β-nicotinamide adenine dinucleotide 3- phosphate), DTNB [5,5-dithio-bis(2-nitrobenzoic acid)], EDTA (Ethylenediamine- Tetra Acetic acid disodium salt dihydrate), TBA (2-Thiobarbituric Acid), TCA (Trichloroacetic Acid), Glutathione reduced, Glutathione oxidized, Methionine, Riboflavin are purchased from Himedia, Mumbai, India. Hydrogen peroxide was purchased from Fisher Scientific Mumbai, India. All other chemicals were of analytical grade and were purchased commercially.

2.2 Preparation of Pod Extract

The fresh pod of *M. oleifera* was purchased from local market of Bilaspur, Chhattisgarh, India and authenticated by qualified Botanist from Guru Ghasidas University, Bilaspur, India. The fruits were washed to remove dirt, cutted in to small pieces and air dried for 7-8 days at RT. Dried fruit were grounded in to powder and 30 gm was extracted by aqueous solvent using soxhlet extractor for 7-8 hours at temperature lower than boiling point of water. The extracts were than evaporated to get solid powder and stored at 4° C for further use.

2.3 Animals

All animal experiments were performed after the approval of institutional animal ethical committee and animal regulatory body of government (Regd. No. 1321/PO/ReBi/10/CPCSEA).

All male wistar rats (100-150g) were divided into seven groups each group containing six rats. All animals were maintained under controlled environment of 22±2° C and 12 hour light and dark cycle. All animals were placed in bed of rice husk and fed with standard pellet diet and water *ad libitium*.

2.4 Experimental Design

Total duration of experiment was designed for 14 days. All animals were divided in to 7 groups as follows:

Group 1: Normal control, given no treatment in experimental duration.

Group 2: Vehicle control, given 0.9% saline (i.p.) on day of cisplatin treatment.

Group 3: Cisplatin control, given Cisplatin (12 mg/kg BW in normal saline) (i.p.) on day 11th of treatment.

Group 4: Pod extracts control, given 200 mg/kg BW of *M. oleifera* aqueous pod extract (*via* oral gavage) for 13 days of treatment.

Group 5: Pod extracts control, given 400 mg/kg BW of *M. oleifera* aqueous pod extract (*via* oral gavage) for 13 days of treatment.

Group 6: Given 200 mg/kg BW of *M.oleifera* aqueous pod extract (*via* oral gavage) for 13 days of treatment and Cisplatin (12 mg/kg BW) on day 11th of treatment.

Group 7: Given 400 mg/kg BW of *M.oleifera* aqueous pod extract (*via* oral gavage) for 13 days of treatment and Cisplatin (12 mg/kg BW) on day 11th of treatment.

On 14th day of experiment blood samples were collected by puncturing retro-orbital venous sinus and allowed to clot at 37° C for 40 minutes and centrifuged at 3000 rpm for 20 minutes for separation of serum. Isolated serum was stored at 4° C for estimating BUN and creatinine level. After blood collection, all animals were sacrificed for isolation of Kidney samples. Kidney samples were immediately weighed and one part was stored at -80° C to study biochemical parameters. And other part is fixed in Bouin's fixative for histopathological study.

2.5 Tissue Homogenate Preparation

The kidney samples were homogenized using motor pestle in phosphate buffer saline (0.05M, pH 7.0) so as to obtain

10% homogenate. The homogenate was centrifuged at 17000 g for 1hr at 4° C and the supernatant was separated into different tubes to study biochemical parameters for assessment of nephroprotector activity of pod extracts.

2.6 Serum Analysis

The function of renal tissue was determined by assessment of serum analysis of Blood Urea Nitrogen level (BUN) and Creatinine level in rat blood. Serum analysis was done using auto-blood analyzer (Erba Diagnostics Mannheim GmbH., Mannheim, Germany) using Urea assay kit (Auto span), purchased from Arkray healthcare Pvt. Ltd., Gujrat, India, and Creatinine assay kit (Erba), purchased from Transasia Bio-medicals Ltd., Solan, H.P. India, respectively.

2.7 Estimation of Total Protein in Kidney Tissue

Total protein content in tissue was determined by the method of Lowry *et al.*[17].

2.8 Assessment of Oxidative Stress Markers

To study oxidative stress markers, activities of following free radical scavenging enzymes were assayed: Superoxide Dismutase (SOD), Glutathione Peroxidase (GPx) and Catalase (CAT) according to the methods previously described (Masayasu and Hiroshi[18], Paglia and Valentine[19] and Cohen *et al.*,[20]) respectively.

2.9 Estimation of Lipid Per-Oxidation (LPO)

As an index of lipid peroxidation the concentration of MDA (Malondialdehyde) in kidney tissue was determined by method of Ohkawa *et al.*,[21] using molar extinction coefficient of 1.56 x 10^5 M^{-1} cm^{-1} and the results are expressed as n moles of MDA/g of tissue.

2.10 Histopathological Study

For histopathological study kidney of all animals of each groups were fixed in Bouin's fixative for 48 hrs, dehydrated in graded alcohol series, cleared in xylene and molded in paraffin wax. Fine sections (4-5 µm) were cut using a microtome (Leica RM 2125 RTS), mounted on glass slides and stained with eosin- hematoxylin and examined under light microscope (10X magnification equipped with a digital camera (Leica DM IL LED) to study histopathological changes.

2.11 Statistical Analysis

The data of all biochemical assays was analyzed by one-way Analysis of Variance (ANOVA) using Minitab 17 software. $P \leq 0.05$ were considered as statistically significant. Values are represented as Mean ± SEM.

3. Results

3.1 Serum Analysis

As shown in Table 1 there is significant increase ($p \leq 0.01$) in both Creatinine and BUN level in cisplatin treated group, however there is no significant changes in groups given different doses of pod extracts only, when compared to normal control group. Treatment with above doses of pod extract in groups given single dose of cisplatin showed only lower dose (200 mg/kg BW) able to significantly ($p \leq 0.01$) reduce the enhanced Creatinine and BUN when compared to cisplatin group.

Table 1. Effect of pod extracts in cisplatin induced renal Creatinine and Blood Urea Nitrogen (BUN)

Groups	Creatinine (mg/dl)	BUN (mg/dl)
Normal Control	0.77 ± 0.06^{ns}	$22.785\pm1.07^{*}$
Vehicle Control	0.82±0.04	15.74±0.06
Cisplatin	$1.96\pm0.10^{**}$	$69.04\pm3.81^{**}$
MAQ 200mg/kg	0.80 ± 0.01^{ns}	15.55 ± 0.09^{ns}
MAQ 400mg/kg	0.69 ± 0.08^{ns}	15.51 ± 0.37^{ns}
MAQ 200+Cis	$1.22\pm0.13^{\#}$	$23.63\pm1.71^{\#\#}$
MAQ 400+Cis	2.08 ± 0.13^{NS}	61.33 ± 2.59^{NS}

Values are expressed as mean ± SE, n=6. $^{***}P \leq 0.001$ vs vehicle control, $^{**}P \leq 0.01$ vs vehicle control, $^{*}p \leq 0.05$ vs vehicle control, $^{\#\#\#}p \leq 0.001$ vs cisplatin, $^{\#\#}p \leq 0.01$ vs cisplatin, $^{\#}p \leq 0.05$ vs cisplatin, ns= non significant vs vehicle control, NS= non significant vs cisplatin.

3.2 Oxidative Stress Marker Analysis

Cisplatin induced renal toxicity mainly involves oxidative stress, hence study of enzymatic and non-enzymatic markers of oxidative stress can be useful for assessment of renal toxicity induced by cisplatin. The effect of cisplatin and fruit extract treated rats was shown in Table 2. A single dose of cisplatin (12mg/kg BW) significantly induces oxidative stress in renal tissue as depicted by

decrease in activities of various enzymatic antioxidants (such as CAT, SOD and GPx) and enhanced the level of nonenzymatic marker of oxidative stress i.e., renal MDA (Malondialdehyde) level. The effect of above doses of pod extracts in above markers of oxidative stress was follows:

3.2.1 Effect on Catalase Activity (CAT)

Treatment of rats with above doses of pod extract showed that the higher dose (400 mg/kg) itself lowers the Catalase activity. However, treatment with lower dose (200 mg/kg BW) significantly ($p \leq 0.05$) enhanced the Catalase activity when compared to cisplatin treated group (Table 2).

3.2.2 Effect on Super Oxide Dismutase Activity (SOD)

As shown in Table 2 treatment of above doses of pod extracts showed no significant difference in activity of SOD in pod extract treated group only when compared to normal control group. However, only the lower dose (200 mg/kg BW) able to significantly ($p \leq 0.01$) reduces the effect of cisplatin in SOD activity.

3.2.3 Effect on Glutathione Peroxidase Activity (GPx)

Treatment of rats with above doses of pod extracts significantly ($p \leq 0.05$) enhanced the GPx activity than normal level in groups given fruit extract only. Treatment with fruit extract in cisplatin treated group showed both doses causes significant ($p \leq 0.001$) increase in activity of GPx when compared to cisplatin group Table 2.

3.2.4 Effect on Lipid Peroxidation (LPO)

Cisplatin treated group has significantly ($p \leq 0.05$) enhanced MDA level. However, groups given pod extract only showed no significant changes in MDA level when compared to normal control group. Treatment with pod extract in cisplatin injected group showed that lower dose cannot reduce the MDA level, whereas higher dose significantly ($p \leq 0.01$) reduces the enhanced MDA level (Table 2).

3.3 Histopathological Study

Hematoxylin and Eosin (H & E) staining of Kidney sections of all groups (Figure 1) showed a single dose of 12mg/kg BW of cisplatin caused severe damage in rat kidney. There is widespread necrosis, polymorphic nuclei are visible, sloughing of Bowman's capsule and degeneration of glomerulus, dilation in proximal and distal convoluted tubules and sloughing of epithelial cells. However, the kidney of control groups and pod extract control groups showed no pathological changes. The groups treated with different doses of pod extracts showed slight necrosis, sloughing of Bowman's capsule and degeneration of glomerulus in higher dose (400 mg/kg BW), however, slight dilation of proximal and distal tubule and sloughing of epithelial cells are marked in both doses when compared to cisplatin treated group, suggesting that high dose of pod extract was may be toxic to kidney.

4. Discussion

Chemotherapeutic treatment of cisplatin is most effective for wide range of tumors. It is more effective in higher doses however; high doses side effects such as nephrotoxicity limits its use in higher doses. From experimental research group it is suggested that a single dose of cisplatin greater than 5 mg/kg body weight in rats cause severe renal toxicity[22–24]. The toxic effects of high doses of cisplatin in Kidney include decrease in glomerular fil-

Table 2. Effect of pod extracts in cisplatin induced renal oxidative stress

Groups	Catalase(U/mg protein)	SOD(%NBT reduction/min)	GPx (U/g tissue)	Conc. Of MDA (n moles/g tissue)
Normal Control	31.40 ± 0.06^{ns}	36.44 ± 1.361^{ns}	51.28 ± 0.89^{ns}	20.95 ± 0.22^{ns}
Vehicle Control	35.71 ± 1.65	35.17 ± 3.307	32.65 ± 3.80	15.34 ± 1.74
Cisplatin	$22.45\pm0.47^{*}$	$16.12\pm1.157^{*}$	$12.83\pm1.37^{*}$	$28.06\pm0.21^{*}$
MAQ 200mg/kg	28.05 ± 0.18^{ns}	57.26 ± 3.777^{ns}	$68.14\pm2.34^{*}$	22.06 ± 0.21^{ns}
MAQ 400mg/Kg	$17.8\pm0.56^{*}$	29.33 ± 0.078^{ns}	$76.42\pm0.68^{*}$	10.95 ± 0.20^{ns}
MAQ 200+ Cis	$39.11\pm0.76^{\#}$	$49.05\pm1.696^{\#\#}$	$73.54\pm0.84^{\#\#\#}$	29.55 ± 0.33^{NS}
MAQ 400+ Cis	19.70 ± 0.29^{NS}	13.67 ± 0.846^{NS}	$61.13\pm1.60^{\#\#}$	$12.82\pm0.76^{\#\#}$

Values are expressed as mean ± SE, n=5. $^{*}p \leq 0.05$ vs vehicle control, $^{\#\#\#}p \leq 0.001$ vs cisplatin, $^{\#\#}p \leq 0.01$vs cisplatin, $^{\#}p \leq 0.05$ vs cisplatin, ns= non significant vs vehicle control, NS= non significant vs cisplatin.

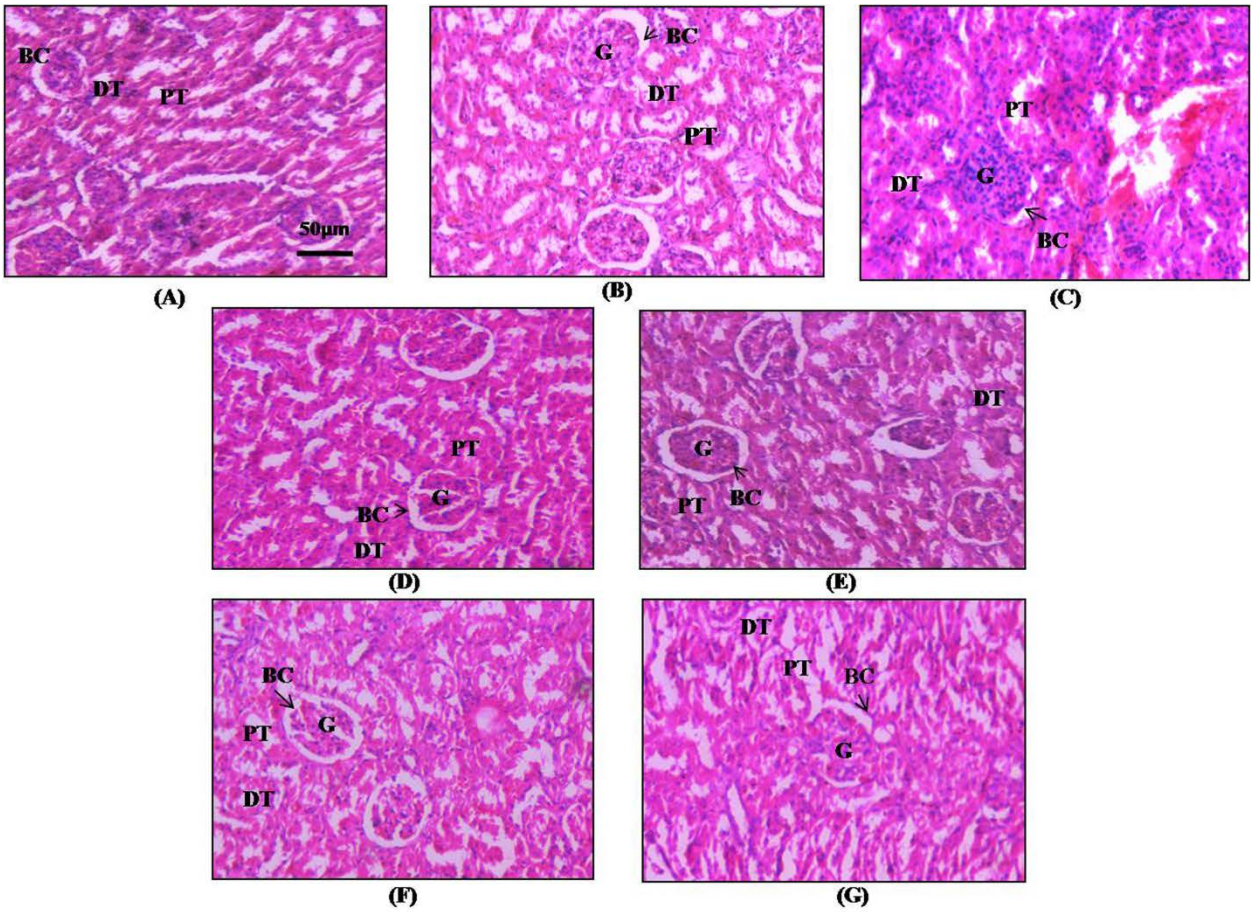


Figure 1. Histopathological Study: (A) Normal Control (B) Vehicle Control (C) Cisplatin (D) MAQ 200mg/kg BW (E) MAQ 400mg/kg BW (F) MAQ 200mg/kg BW + Cisplatin (G) MAQ 400mg/kg BW + Cisplatin. MAQ= Moringa aqueous extract; G = Glomerulus; BC = Bowman's capsule; DT = Distal Tubule; PT = Tubule. Scale bars are equivalent of 50 µm.

tration, increased creatinine and BUN, increase in lipid peroxidation, decrease in enzymatic and non enzymatic antioxidants[25].

The present investigation explores the protective effects of *M. oleifera* pods in cisplatin induced oxidative stress and degeneration of renal tissue. The present work showed that *M. oleifera* aqueous pods extracts restored the kidney dysfunction markers which were disturbed by cisplatin treatment. Histopathological study also supports the preventive effect against nephrotoxicity of *M. oleifera* pods.

A single dose of cisplatin (12mg/kg BW) significantly enhanced the activities of serum Creatinine and BUN level. It is reported that level of serum creatinine and BUN was enhanced in those taking nephrotoxic medicines[26]. The increase in creatinine was may be due to up regulation of Guanidinoacetate Methyltransferase (GAMT)[27]. Treatment with lower (200 mg/kg BW) and higher dose (400mg/kg BW) of *M. oleifera* aqueous pod extracts showed that lower dose was only significantly reducing the creatinine and BUN level when compared to cisplatin group however, the level of creatinine was remains higher than normal values (Table 1).

Some studies have suggested that the main mechanism behind cisplatin induced nephrotoxicity involve oxidative stress[4]. A single dose of cisplatin more than 5 mg/kg body weight cause deterioration of antioxidant defense system as evidenced by decrease in activities of CAT, SOD and GPx. Reports from other studies suggest that CAT activity was more vulnerable than SOD activity or GPx activity in cisplatin induced nephrotoxicity[28]. The increase in MDA level was in correlation with decrease in antioxidant enzymes. In this study a single dose of cisplatin (12 mg/kg BW) caused significant decrease in

activities of above enzymes and increase in MDA level (Table 2). Treatment with lower (200 mg/kg BW) and higher dose (400mg/kg BW) of *M. oleifera* aqueous pod extracts showed the lower dose is significant effective in enhancing the activities of above enzymes and not involve in lipid peroxidation. However, higher dose is only effective in activity of GPx and lipid peroxidation, it is also showed that the higher dose significantly reduces the CAT activity when compared to normal groups. As shown in Table 2, higher dose also enhances the activity of GPx than normal values. The previous studies also showed *M. Oleifera* pod extracts showed strong antioxidative capacity and involved in enhancing antioxidative enzymes and lowering lipid peroxidation[15,16,29,30]. Histopathological examination of kidney sections of all groups showed that the antioxidant activity of pod extracts partially repairs the renal tissue damage and among the both doses, lower dose showed less damage comparing to cisplatin group, thus supporting the above biochemical parameters.

5. Conclusion

In summary, the present study showed the aqueous pod extract of *M. oleifera* may have protective effect against cisplatin induced nephrotoxicity. The protective effect was mainly by alleviating antioxidant defense and thus reducing oxidative stress. The protective effect was significant in lower dose; however, higher dose may be toxic to antioxidative enzymes. The findings suggest that the lower dose of *M. oleifera* pod extract can reduce the toxic effects of cisplatin and thus can be used as adjuvant in cancer therapy. However, further investigation is required to evaluate its complete protective capability against cisplatin induced nephrotoxicity.

6. Acknowledgement

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7. Conflict of Interest

No conflict of Interest.

8. References

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