

Full Length Research Paper

## Protective effects of aqueous extract of *M. pruriens* Linn. (DC) seed against cisplatin induced oxidative stress and nephrotoxicity in rats

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In the present study, we investigated the effect of the aqueous extract of *Mucuna pruriens*, against cisplatin induced oxidative stress and nephrotoxicity in rats. Nephrotoxicity was induced by a single dose of cisplatin (5 mg/kg body weight *i.p.*). Cisplatin administration resulted in significant increases in urine volume, serum creatinine and urea and significant decrease in creatinine clearance and urinary sodium in comparison with control. Also, the renal tissue from the cisplatin treated rats showed significant decreases in the kidney glutathione content, superoxide dismutase and catalase activity and a significant increase in lipid peroxides levels. Seven days after *M. pruriens* extract at a dose of 200 and 400 mg/kg plus cisplatin treatments significantly decrease urea, creatinine and significantly increase creatinine clearance levels as compared to cisplatin rats in a dose dependent manner. In addition, *M. pruriens* prevented the rise of lipid peroxides and the reduction of superoxide dismutase, catalase and glutathione activities in a dose dependent manner. These results suggest that *M. pruriens* extract has protective effects against cisplatin induced oxidative stress and nephrotoxicity in rats.

**Key words:** *Mucuna pruriens*, cisplatin, lipid peroxidation, free radicals.

### INTRODUCTION

Cisplatin (*cis*-diamminedichloroplatinum II, CP), one of the most potent and widely used anticancer drugs containing platinum, is highly effective against many tumors, including testicular, small cell lung, head and neck, and bladder carcinomas (Meyer et al., 1994). However, the clinical usefulness of this drug is limited by the development of nephrotoxicity, a side effect that may be produced in various animal models (Kim et al., 1997; Gregg et al., 2001; Chirino et al., 2004; Weijl et al., 2004). The xenobiotic-induced alterations in kidney functions are characterized by signs of injury, such as changes in urine volume, creatinine clearance, in glutathione (GSH) status, increase of lipid peroxidation (LPO). Formation of free radicals, leading to oxidative stress, has been shown to be one of the main pathogenic mechanisms of these toxicities and side effects of

nephrotoxicants (Greggi et al., 2000; Atessahin et al., 2003). CP induced nephrotoxicity is also closely associated with an increase in LPO in the kidney tissues. This antitumoural drug causes generation of reactive oxygen species (ROS), such as superoxide anion and hydroxyl radical, to deplete of GSH levels and to inhibit the activity of antioxidant enzymes in renal tissue. ROS may produce cellular injury and necrosis via several mechanisms including peroxidation of membrane lipids, protein denaturation and DNA damage (Kim et al., 1997; Mora et al., 2003). *Mucuna pruriens* Linn. DC. (Leguminosae) is annual climbing legume endemic in India and in other parts of the tropics including Central and South America. In India, the plant is known by different local names like "the cowhage", "velvet" bean and "atmagupta". In Ayurvedic system of medicine, *M.*

*pruriens* was used for the management of male infertility, nervous disorders and also as an aphrodisiac agent (Pandey et al., 1996; Muthu and Krishnamoorthy, 2011). *M. pruriens* seed powder contains high amount of L-DOPA, a potentially neurotoxic agent used in the treatment of parkinson's disease (Pant et al., 1970). *M. pruriens* seed in addition to levodopa, contains tryptamine, 5-hydroxytryptamine (5-HT), mucunine, mucunadine, prurienine and prurieninine (Mehta et al., 1994).

It is also rich in fatty content (Panikkar et al., 1987). Alcoholic extract of seed inhibit iron-induced lipid peroxidation (Tripathi et al., 2002). *M. pruriens* seed extract has been reported to attenuate progression of renal damage in streptozotocin-induced diabetic mice (Grover et al., 2001). In type 1 and type 2 diabetes, renal production of dopamine was reduced (Carranza et al., 2001) and this reduction was associated with an increase in total body sodium and impaired ability to excrete sodium load (Segers et al., 1996). In light of above objective, current investigation was to study effect of *M. pruriens* seed extract in cisplatin induced nephrotoxicity and oxidative stress damage in rats.

## MATERIALS AND METHODS

### Plant Extract

The seeds of *Mucuna pruriens* (L.) DC. (MP) were purchased from the United Chemicals and Allied Products, Kolkata, India. It was authenticated by Dr. B. C. Patel, Botany Department, Modasa, India. A voucher specimen was retained in our laboratory for further reference. For the extract, the seeds were powdered in a mechanical grinder. 1 kg seed powder of *M. pruriens* was initially defatted with 750 ml of petroleum ether (60-80°C) then aqueous extract was prepared by cold maceration method in that extract was shaken intermediately and  $\text{CHCl}_3$  was added to prevent bacterial growth. After seven days, the extract was filtered using Whatman filter paper (No. 1) and then concentrated in vacuum and dried. The yield was 10.05 % w/w with respect to dry powder.

### Standardization of extract

Standardization of extract was carried out by high performance thin layer chromatography. The samples were spotted in the form of bands with a Camag microlitre syringe on a precoated silica gel plates 60 F<sub>254</sub> (20 cm x 10 cm with 0.2 mm thickness, E. Merck, Darmstadt, Germany) using a Camag Linomat V Automatic Sample Spotter (Muttentz, Switzerland).

The plates were prewashed by methanol and activated at 60°C for 5 min prior to chromatography. The plate was developed in a solvent system (6.0 ml) of n-butanol-acetic acid-water (4.0 + 1.0 + 1.0, v/v) in a CAMAG glass twin-through chamber (10 x 10 cm) previously saturated with the solvent for 30 min (temperature 25 ± 2°C, relative humidity 40%). The development distance was 8 cm. Subsequent to the scanning, TLC plates were air dried and scanning was performed on a Camag TLC scanner III in absorbance mode at 280 nm and operated by Win Cats software. Evaluation was via peak areas with linear regression. Calibration curve of standard L-dopa was plotted and was found to be linear in the range of 10-120 µg/ml.

### Experimental animals

Sprague Dawely rats weighing 200-250 g were used for the study. The animals were housed in a group of 3 rats per cage under well-controlled conditions of temperature (22 ± 2°C), humidity (55 ± 5%) and 12 h/12 h light-dark cycle. They were maintained under standard environmental conditions and were fed a standard rat chow diet with water given *ad libitum*. The study was approved by Institutional Animal Ethical Committee, Shri B. M. Shah College of Pharmaceutical Education and Research, Modasa, Gujarat, India (IAEC/BMCPER/02/2005-06).

### Treatment protocols

The rats were divided into five groups; each group containing six rats. CP was injected to animal intraperitoneally at the dose of 5 mg/kg, which is well documented to induce nephrotoxicity in rats (Shimeda et al., 2005; Tebekeme and Prosper, 2007). Group 1 served as control. Group 2 received MP extract (400 mg/kg, p.o.). Group 3 received a single dose CP (5 mg/kg, i.p.). Group 4 received MP extract (200 mg/kg, p.o.) for 6 consecutive days after CP injection. Group 5 received MP (400 mg/kg, p.o.) extract for 6 consecutive days after CP injection. On day 7 after CP injection, blood samples were collected from the tail vein and allowed to clot for 30 min at room temperature. Blood samples were centrifuged at 3000 rpm for 20 min. Serum was separated and stored at -20°C until analysis was done. Serum samples were analyzed spectrophotometrically for urea and creatinine (Bayer Diagnostics Kit, India). The kidneys were removed, washed with ice-cold saline and homogenized in ice cold 0.1 M Tris-HCl buffer (pH 7.4). The homogenate was centrifuged and supernatant was used for the assay of lipid peroxidation (Ohkawa et al., 1979), superoxide dismutase (Mishra et al., 1972), catalase (Aebi et al., 1974), glutathione (Beutler et al., 1963) and total protein estimation (Lowry et al., 1951). The changes in urinary volume were measured at 12 h intervals and the changes in the body weight were also determined throughout the experiments. Urinary sodium was measured by flame photometry. Creatinine clearance was measured according to Jaiswal et al. (1995).

### Statistical analysis

Results were expressed as mean ± standard error of mean (S.E.M.). Result were analyzed statistically using analysis of variance (ANOVA) followed by Tukey's test. Values of p < 0.05 were considered significant.

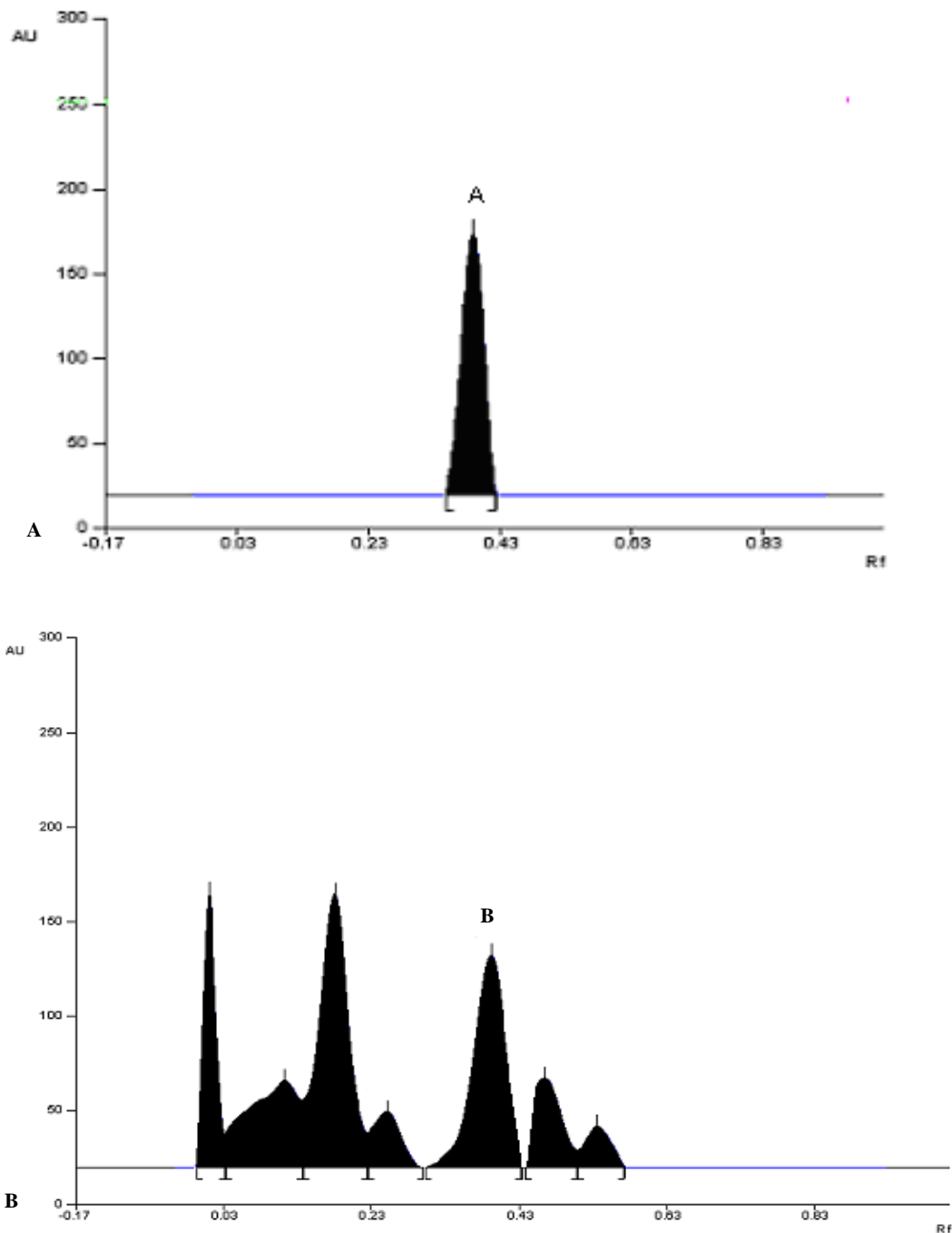
## RESULTS

### Standardization of extract

The concentration of L-dopa in aqueous extract of *M. pruriens* was found to be 5.6%. Comparison of absorption spectrum of the band in the sample track with that of standard L-dopa at R<sub>f</sub> 0.39 by overlapping confirmed the presence of L-dopa in the sample and it was found to be one of the major components (Figure 1).

### Effect on body weight and urine volume

Rats which received CP showed a marked decrease in body weight, urinary sodium and increase urine volume



**Figure 1.** Densitograms of (A) Standard L-dopa (B) a typical seed extract of *Mucuna pruriens* ( $R_f$  value = 0.39).

as compared to control rats. Treatment with aqueous extract at a dose of 200 and 400 mg/kg did not show any significant change in body weight as compared to CP treated rats. *M. pruriens* seed extract at a dose of 400 mg/kg significantly increase urine volume and urinary sodium as compared to CP rats. However, increase in urine volume and urinary sodium at 200 mg/kg of aqueous extract of *M. pruriens* was not significant (Table 1).

#### **Effect on serum urea, creatinine and creatinine clearance**

Cisplatin treated rats showed a significant increase serum urea, creatinine and decrease creatinine clearance levels as compared to control rats. Aqueous extract significantly decrease serum urea and creatinine levels and increase creatinine clearance levels as compared to CP treated rats in a dose dependent manner (Table 1).

**Table 1.** Effects of aqueous extract of *M. pruriens* on various parameters in cisplatin induced nephrotoxicity in rats.

Parameter	Control	MP 400 mg/kg	CP	CP +MP 200 mg/kg	CP +MP 400 mg/kg
Body weight (g)	223 ± 10.06	225 ± 9.98	185 ± 4.46*	206 ± 6.99	212 ± 8.44
Urine volume (ml/12h)	3.04 ± 0.27	3.18 ± 0.32	16.60 ± 1.06	20.52 ± 1.65	27.98 ± 1.75**
Urinary sodium (mg/ml/12hr)	4.78 ± 0.22	4.79 ± 0.28	1.98 ± 0.33	2.54 ± 0.38	3.93 ± 0.43**
Urea (mg/dl)	40.90 ± 2.99	39.74 ± 3.44	85.80 ± 6.11*	61.94 ± 5.22**	49.78 ± 6.01**
Creatinine (mg/dl)	0.88 ± 0.08	0.87 ± 0.06	1.90 ± 0.08*	1.22 ± 0.07**	1.00 ± 0.08**
Creatinine clearance (ml/min)	0.60 ± 0.03	0.62 ± 0.03	0.26 ± 0.02*	0.40 ± 0.03**	0.56 ± 0.02**

Each value is mean ± S.E.M. (n = 6); \*, Significantly different from normal control, p<0.05; \*\*, significantly different from cisplatin control, p<0.05.

**Table 2.** Effects of aqueous extract of *M. pruriens* seed extract on lipid peroxidation and antioxidant parameters in cisplatin induced nephrotoxicity in rats.

Parameter	Control	MP 400 mg/kg	CP	CP +MP 200 mg/kg	CP +MP 400 mg/kg
Lipid Peroxidation (µmole/mg of protein)	0.89 ± 0.11	0.90 ± 0.13	5.84 ± 0.48*	3.91 ± 0.35**	2.37 ± 0.33**
Superoxide dismutase (U/min/mg of protein)	0.53 ± 0.06	0.52 ± 0.05	0.21 ± 0.03*	0.37 ± 0.04**	0.51 ± 0.04**
Catalase (U/mg of protein)	19.94 ± 2.22	19.78 ± 1.84	9.42 ± 1.01*	16.50 ± 1.77**	19.89 ± 1.72**
Glutathione (µ mole/ mg of protein)	1.53 ± 0.15	1.50 ± 0.17	0.38 ± 0.15*	0.99 ± 0.12**	1.39 ± 0.14**

Each value is mean ± S.E.M. (n = 6); \*, Significantly different from normal control, p<0.05; \*\*, significantly different from cisplatin control, p<0.05.

### Effect on lipid peroxidation and antioxidant parameters

Administration of CP in rats produced a significant increase in lipid peroxides and significant decrease in superoxide dismutase, catalase and glutathione levels in kidney tissue as compared to control rats. Treatment with aqueous extract at a dose of 200 and 400 mg/kg significantly decrease lipid peroxides and increase in superoxide dismutase, catalase and glutathione levels in a dose dependent manner as compared to CP treated rats. Aqueous extract alone in rats did not produce any significant change in lipid peroxides and antioxidant parameters in kidney tissue (Table 2).

### DISCUSSION

In the present study, the rats treated with CP showed a decrease in body weight. This weight loss was attenuated, but not completely with aqueous extract of *M. pruriens*. Mora et al. (2003) reported suggested that CP

induced weights loss might be due to gastrointestinal toxicity and by reduced ingestion of food.

The impairment of kidney function by CP is recognized as the main side effect and the most important dose limiting factor associated with its clinical use. Several investigators reported that the alterations induced by CP in the kidney functions were characterized by signs of injury such as, increase urine volume, urea and creatinine level in serum (Greggi et al., 2001; Naziroglu et al., 2004). In the present study, it was shown that administration of CP to rats increased urine volume, serum creatinine and serum urea and decrease in creatinine clearance and urinary sodium as compared to control one. Treatment with aqueous extract at a dose of 200 and 400 mg/kg significantly decrease serum urea and creatinine level and significantly increase in creatinine clearance in a dose dependent manner. Aqueous extract at a dose of 400 mg/kg also produced a significant increase in urine volume and urinary sodium which was increase in CP treated rats. This effect may be due to presence of L-dopa in the extract because it binds with dopamine receptors. D<sub>1</sub>-like receptors are reported

to cause an increase in renal blood flow and glomerular filtration rate, as well as increase in urinary excretion of water and sodium (Hedge et al., 1989; Jose et al., 1992). Several studies have shown the role of dopamine in the regulation of sodium excretion during acute volume expansion and during acute increase in sodium intake (Chen et al., 1991; Hedge et al., 1989; Oates et al., 1979).

The concentration of lipid peroxides as a result of lipid peroxidation shows an increase in CP treated group. The decreased superoxide dismutase activity can cause the initiation and progression of lipid peroxidation in the CP treated rats. This decreased activity may be due to loss of copper and zinc, which are essential for the enzyme activity or reactive oxygen species induced enzyme inactivation (Matsushima et al., 1998). Recent evidences have indicated that the free radicals and reactive oxygen species are involved in the CP induced oxidative stress because of depletion of the GSH concentration and decreased antioxidant enzyme activity in the kidneys (Sato et al., 2003; Sharma et al., 1985; Zeki et al., 2003). These observations also support the hypothesis that part of the mechanism of nephrotoxicity in the CP treated animals is related to depletion of antioxidants. In the present study, treatment with aqueous extract of *M. pruriens* at a dose of 200 and 400 mg/kg significantly decrease lipid peroxides and significantly increase the superoxide dismutase and catalase levels as compared CP treated rats in dose dependent manner. Rajeshwar et al. (2005) have reported that alcoholic extract of seed of *M. pruriens* inhibit lipid peroxidation *in vitro*. Alcoholic extract of the seeds of *M. pruriens* has anti lipid peroxidation activity which is mediated through removal of superoxide radical and hydroxyl radical (Tripathi et al., 2002). Aqueous extract of *M. pruriens* contain L-dopa which was reported to decrease free radical generation in various *in vitro* radical scavenging models (Gulcin, 2007).

One of the most important intracellular antioxidant systems is the glutathione redox cycle. GSH is one of the essential compounds for maintaining cell integrity because of its reducing properties and participation in the cell metabolism. The depletion in the renal GSH level has been observed in rats in response to oxidative stress caused by CP treatment (Kim et al. 1997; Silva et al., 2001). On the other hand, results of some investigators showed that the kidney damage caused by CP is not associated with decreased in renal GSH (Greggi et al., 2000) or may causes increase in GSH levels (Mora et al., 2003). The mechanism of this antitumoural drug induced change in renal GSH level is not completely understood. However, GSH may modulate metal reduction and the thiol portion is very reactive with several compounds, mainly with alkylating agents such as CP. In this study, GSH levels in the renal tissue of rats treated with CP were lower than normal control group. On the other hand, an increase in GSH levels in the renal tissue indicates that treatment with aqueous extract of *M. pruriens* was caused in response to oxidative stress.

## Conclusion

In conclusion, our data suggests that aqueous extract of *M. pruriens* protect the CP induced oxidative stress and nephrotoxicity in rats. The mechanism may be attributed to its free radical scavenging property of L-dopa in the extract.

## ABBREVIATIONS

**CP**, Cisplatin (*cis*-diamminedichloroplatinum II, CP); **GSH**, glutathione; **LPO**, lipid peroxidation; **ROS**, reactive oxygen species; **5-HT**, 5-hydroxytryptamine.

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