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RESEARCH ARTICLE

Protective effects of aqueous extract of *Mucuna pruriens* Linn. (DC) seed against gentamicin-induced nephrotoxicity and oxidative stress in rats

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ABSTRACT

In the present study, we investigated the effects of aqueous extract of *Mucuna pruriens* on gentamicin (100 mg/kg/day for six days)-induced nephrotoxicity and oxidative stress in rats. Gentamicin-induced nephrotoxicity was evidenced by marked (p<0.05) increase in serum urea and creatinine levels and urine volume and decrease in urinary sodium levels and creatinine clearance (p<0.05). Use of *M. pruriens* extract at a dose of 200 mg/kg and 400 mg/kg alonge with gentamicin caused a dose dependant decrease (p<0.05) in serum creatinine and urea levels and an increase (p<0.05) in creatinine clearance. There was a significant (p<0.05) increase in the urinary sodium levels by *M. pruriens* extract at a dose of 400 mg/kg but not at the dose of 200 mg/kg when compared with gentamicin control rats. Treatment with *M. pruriens* extract at a dose of 400 mg mg/kg further increased (p<0.05) the urine volume as compared to gentamicin control rats. However, further increase in urine volume by *M. pruriens* extract at a dose of 200 mg/kg was not significant. Renal oxidative stress was determined by renal lipid peroxides levels, glutathione (GSH) levels and by enzymatic activity of superoxide dismutase (SOD) and catalase (CAT). Gentamicin caused significant (p<0.05) increase in lipid peroxide levels and significant (p<0.05) decrease in GSH levels and SOD and CAT activity. *M. pruriens* extract significantly (p<0.05) and dose-dependently reduced lipid peroxidation and enhanced GSH levels and SOD and CAT activities. Our data suggest that *M. pruriens* extract has protective potential against gentamicin-induced nephrotoxicity and oxidative stress in rats.

Keywords: *Mucuna pruriens; gentamicin; nephrotoxicity; lipid peroxidation; free radical*

Aminoglycoside antibiotics, especially gentamicin are widely applied in veterinary and human clinical practices for treatment of life-threatening gram negative infections [1]. These antibiotics also cause a dose-dependent drug-induced nephrotoxicity in 10–20% of therapeutic courses. Therefore, the clinical usefulness of these drugs is limited by the development of nephrotoxicity, a side effect produced in various animal models. Gentamicin -induced nephrotoxicity is characterized by direct tubular necrosis, without morphological changes in glomerular structures [2]. The investigations indicate more frequent nephrotoxicity in the patients treated with gentamicin than in those treated with other aminoglycosides. Gentamicin undergoes more extensive accumulation in kidneys, and it is trapped by renal cortex cells via different mechanism [3,4].

The real mechanism by which gentamicin induces nephrotoxicity is unknown, however, it has been shown both *in-vitro* and *in-vivo* studies to enhance the generation of reactive oxygen species (ROS). Abnormal production of ROS may damage some macromolecules and induce cellular injury and necrosis via several mechanisms including peroxidation of membrane lipids, protein denaturation and DNA damage. This is believed to be involved in the etiology of many xenobiotics toxicity [5,6]. The alteration in kidney functions induced by lipid peroxidation is a proximal event in the injury cascade of genatmicin nephrotoxicity. Some investigators showed that genatmicin acts as an iron chelator, and that the iron- genatmicin complex is a potent catalyst of free radical formation [7].

Mucuna pruriens Linn. DC. (Leguminosae) known as ‘‘the cowhage’’ or ‘‘velvet’’ bean and ‘‘atmagupta’’ is a climbing legume endemic in India and in other parts of the tropics including Central and South America. In Ayurvedic system of medicine, *M. pruriens* was used

for the management of male infertility, nervous disorders and also as an aphrodisiac [8]. *M. pruriens* seed powder contains high amount of L-dopa, which is a neurotransmitter precursor and effective remedy for the relief in Parkinson's disease [9]. *M. pruriens* seed in addition to L-dopa, contains tryptamine, 5-hydroxytryptamine (5-HT), mucunine, mucunadine, prurienine and prurieninine [10]. Alcoholic extract of *M. pruriens* reported to inhibit *in-vitro* iron-induced lipid peroxidation [11]. *M. pruriens* seed extract has been reported to attenuate progression of renal damage in streptozotocin-induced diabetic mice [12]. In type 1 and type 2diabetes, renal production of dopamine was reduced [13] and this reduction was associated with an increase in total body sodium and impaired ability to excrete sodium load [14]. In light of above objective, current investigation was carried out to study effect of *M. pruriens* seed extract in gentamicin-induced nephrotoxicity and oxidative stress in rats.

MATERIALS AND METHODS

Plant extract

The seeds of *M. pruriens* Linn. (DC) 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 (Voucher No. BMCPER-0116). For the extract, the seeds were powdered (particle size ~ 0.25 mm) in a mechanical grinder. One 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 $CHCl_3$ was added to prevent bacterial growth. After seven days, the extract was filtered using Whatman filter paper (No. 1) and then concentrated under reduced pressure (bath temp. 50^0C) and finally dried in a vacuum desiccator. 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 (HPTLC). The samples were spotted in the form of bands with a Camag microlitre syringe on a precoated silica gel plates 60 F_{254} (10 cm ×10 cm with 0.2 mm thickness, E. Merck, Darmstadt, Germany) using a Camag Linomat V Automatic Sample Spotter (Muttenz, 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^oC, 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. L-dopa content in aqueous extract was determined from calibration curve.

Experimental animals

Male 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 12h/12h 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. Gentamicin was injected to animals intraperitoneally at the dose of 100 mg/kg for six consecutive days which is well documented to induce nephrotoxicity in rats [2,4,5]. Group 1 served as control and received saline solution. Group 2 received *M. pruriens* extract (400 mg/kg, p.o.) for 6 days. Group 3 received genatmicin (100 mg/kg i.p.) once daily for 6 days. Group 4 received genatmicin (100 mg/kg i.p.) and *M. pruriens* (200 mg/kg, p.o.) simultaneously for 6 days. Group 5 received genatmicin (100 mg/kg i.p.) and *M. pruriens* (400 mg/kg, p.o.) extract simultaneously for 6 days.

At the end of six days, blood samples were collected from the tail vein after 8 h fasting and allowed to clot for 30 minutes at room temperature. Blood samples were centrifuged at 3000 rpm for 20 minutes. Serum was separated and stored at -20°C until biochemical estimations were carried out. 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 [15], superoxide dismutase [16], catalase [17], glutathione [18] and protein estimation [19]. The changes in urinary volume were measured at 12h intervals and the changes in the body weight were also determined throughout the experiments. Urinary sodium was measured by flame photometry [20]. Creatinine clearance was measured according to Jaiswal [21].

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.

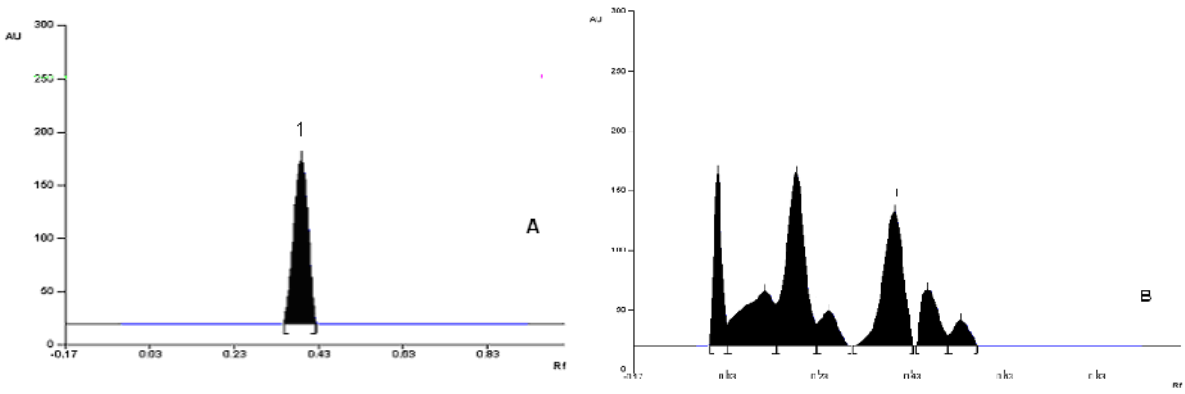

Fig. 1. HPTLC Chromatograms of (A) Standard L-dopa (B) a Typical Seed Extract of *Mucuna pruriens*
Key to peak identity: 1, L-dopa

RESULTS

Standardization of extract

The concentration of L-dopa in the aqueous extract of *M. pruriens* was found to be 5.6%. Comparision of absorption spectrum of the band in the sample track with that of standard L-dopa at R_f 0.39 by overlaping confirmed the presence of L-dopa in the sample and it was found to be one of the major components (Fig. 1).

Effect on body weight, urine volume and urinary sodium

Rats which received genatmicin showed a marked decrease in body weight and urinary sodium and increase in urine volume as compared to control rats. *M. pruriens* extract did not show any significant change in body weight as compared to genatmicin control rats. Urinary sodium levels was significantly (p<0.05) increased in rats treated with *M. pruriens* extract at a dose of 400 mg/kg but not at the dose of 200 mg/kg. *M. pruriens* seed extract at a dose of 400 mg/kg further increased (p<0.05) the urine volume as compared to genatmicin control rats. However, furhter increase in urine volume at a dose of 200 mg/kg of *M. pruriens* extract was not significant (Table. 1).

Effect on serum urea, creatinine and creatinine clearance

Genatmicin administration produced a significant (p<0.05) increase serum urea and creatinine levels as compared to control rats. *M. pruriens* extract at a dose of 200 mg/kg and 400 mg/kg showed marked reduction in serum urea and creatinine levels as compared to genatmicin control rats. The reduction produced by aqueous extract on serum urea and creatinine was dose dependant. There was a significant (p<0.05) decrease in the creatinine clearance in genatmicin control rats when compared with the control one. The decrease in creatinine clearance was significantly (p<0.05) prevented in animals treated with *M. pruriens* extract in a dose dependant manner (Table. 1).

Effect on lipid peroxidation and antioxidant parameters

Lipid peroxides, the end product of lipid peroxidation was significantly (p<0.05) higher in the kidney tissue of genatmicin control rats as compared to control rats. *M. pruriens* extract at a dose of 200 mg/kg and 400 mg/kg caused a dose-dependant decrease in lipid peroxides which were increased in genatmicin control rats. Genatmicin control rats also showed a significant (p<0.05) decrease in superoxide dismutase (SOD), catalase (CAT) and glutathione (GSH) levels in the kidney tissue as compared to control rats. Treatment with *M. pruriens* extract produced dose dependant increase in superoxide dismutase, catalase and glutathione levels. Aqueous extract alone in rats did not produce any significant change in lipid peroxides and SOD, CAT and GSH in kidney (Table 2).

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

Parameters	Control	MP 400 mg/kg	GEN	GEN +MP 200 mg/kg	GEN +MP 400 mg/kg
Body weight (g)	234 ± 9.78	232 ± 10.06	196 ± 4.57*	207 ± 9.80	213 ± 9.01
Urine volume (ml/12h)	3.54 ± 0.41	3.82 ± 0.50	15.32 ± 1.46*	19.96 ± 1.57	26.56 ± 2.14**
Urinary sodium (mg/ml/12hr)	4.08 ± 0.39	4.24 ± 0.29	2.01 ± 0.41*	2.56 ± 0.40	3.68 ± 0.47**
Urea (mg/dl)	36.49 ± 2.21	37.15 ± 3.36	62.74 ± 5.43*	46.30 ± 3.04 **	41.95 ± 2.80**
Creatinine (mg/dl)	0.90 ± 0.06	0. 89 ± 0.05	1.77 ± 0.09*	1.26 ± 0.06**	1.07 ± 0.07**
Creatinine clearance (ml/min)	0.56 ± 0.02	0.60 ± 0.04	0.24 ± 0.02*	0.39 ± 0.03**	0.53 ± 0.03**

Each value is mean ± S.E.M. (n = 6)
* Significantly different from normal control, p<0.05
**Significantly different from gentamicin control, p<0.05
MP: *M. pruriens* extract

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

Parameters	Control	MP 400 mg/kg	GEN	GEN +MP 200 mg/kg	GEN +MP 400 mg/kg
Lipid Peroxidation (μmole/mg of protein)	0.94 ± 0.08	0.92 ± 0.12	6.01 ± 0.40*	4.15 ± 0.41**	2.92 ± 0.39**
Superoxide dismutase (U/min/mg of protein)	0.55 ± 0.06	0.54 ± 0.06	0.22 ± 0.03*	0.39 ± 0.03**	0.49± 0.04**
Catalase (U/mg of protein)	18.99 ± 2.05	19.57 ± 1.95	8.96 ± 1.01*	14.72 ± 1.52**	19.49 ± 1.85**
Glutathione (μ mole/ mg of protein)	1.30 ± 0.14	1.32 ± 0.18	0.30 ± 0.07*	0.89 ± 0.09**	1.22 ± 0.11**

Each value is mean ± S.E.M. (n = 6)
* Significantly different from normal control, $p<0.05$
**Significantly different from gentamicin control, $p<0.05$
MP: *M. pruriens* extract

DISCUSSION

Gentamicin is an aminoglycoside widely used in clinical practice for the treatment of gram-negative infections. Although this drug has proven its usefulness, its nephrotoxic action limits the extent of its use. The onset of damaging renal function induced by genatmicin occurs after 5–7 days treatments between 80 and 150 mg/kg. In this study, genatmicin was injected intraperitoneally at the dose of 100 mg/kg, for six successive days, which is well known to cause significant nephrotoxicity in rats [4,5,22]. Nephrotoxicity of the drugs is associated with their accumulations in renal cortex, dependent upon their affinity to kidneys and on kinetics of drug trapping processes. From the morphological perspective, aminoglycosides bind to cell membranes of proximal tubules, and then the drug is transported to interior of the cells by pinocytosis [3,4]. Several investigators reported that treatments with genatmicin produce nephrotoxicity, evident by the reduction in renal functions which is characterized by an increase in serum creatinine and urea levels accompanied by impairment in glomerular functions [6, 23]. Serum creatinine level is more significant than the urea levels in the earlier phase of the renal damage. In the present study, it was found that treatment with genatmicin alone to rats caused nephrotoxicity, which was correlated with increased urine volume, creatinine and urea levels and decreased urine sodium and creatinine clearance possibly by the reduction in glomerular filtration rate. Treatment with *M. pruriens* extract at a dose of 200 mg/kg and 400 mg/kg significantly decreased serum urea and creatinine and significantly increased creatinine clearance in a dose dependent manner, indicating an increase in the glomerular filtration rate. *M. pruriens* extract at a dose of 400 mg/kg significantly increased urinary sodium as compared GEN control rats. Alcoholic extract of *M. pruriens* attenuated the progression of renal damage by decrease urine volume and urine albumin levels which was increase in STZ-diabetic mice [14]. In our study, *M. pruriens* extract at a dose of 400 mg/kg further increased the urine volume as compared to GEN control rats and this effect may be due to presence of L-dopa in the extract because the effects of L-dopa were linked to endorenal dopamine synthesis and to dopamine-1 receptor stimulation [24]. D_1-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 [25].

The exact mechanism of gentamicin-induced nephrotoxicity is unknown; however, several investigators reported that aminoglycoside antibiotics are a class of drug capable of causing the formation of ROS which can be directly involved in genatmicin-induced damage. MDA, end product of lipid peroxidation in tissues, results in a decrease in polyunsaturated fatty acid content, which serves as substrate for free radicals. The interaction between cationic drugs such as aminoglycosides, with the anionic phospholipid is considered the first step for the development of genatmicin toxicity [3,4]. On the other hand, some authors reported that iron is important in models of tissue injury, presumably because it is capable of catalyzing free-radical formation. Genatmicin and some antibiotics act as iron chelators and cause release of iron from renal cortical mitochondria. Iron-genatmicin complex is a potent catalyst of free-radical formation which enhances the generation of ROS [5, 7]. A relationship between nephrotoxicity and oxidative stress has been confirmed by many investigations. The impairment in kidney functions was accompanied by either increase in serum creatinine and urea levels or kidney tissue MDA levels that indicate lipid peroxidation [2,26].

Gentamicin-induced nephrotoxicity was associated with low activity of GSH-peroxidase, CAT, SOD and levels of GSH in the renal cortex. These decreases in renal antioxidant enzymatic protection could aggravate the oxidative damage. The increased production of ROS in GEN-induced nephrotoxicity may cause inactivation of antioxidant enzymes such as GSH-peroxidase, CAT and SOD. Also, it is well established that GEN administration to rats enhances the production of H_2O_2 in renal cortical mitochondria as a result of the increase in the production of O^-_2 and H_2O_2 may interact to form a reactive unstable radical, namely HO^-. It is known that H_2O_2 inactivates GSH-peroxidase and CAT enzymes [3], with reduced activity of one or both leading to an increase in lipid peroxidation [27]. The decrease amount of GSH and the accumulation of H_2O_2 and HO^- are triggering factors in GEN nephrotoxicity. Similarly, in this study, the increases in lipid peroxides levels, decreases in SOD, CAT and GSH activities in GEN control rats appear to support above investigations. *M. pruriens* ex-

tract at a dose of 200 mg/kg and 400 mg/kg caused significant decrease in lipid peroxides levels and significant increase in SOD, CAT and GSH levels in kidney tissue when compared to GEN control group in a dose dependant manner. Tripathi and Upadhyay [11] reported that alcoholic extract of *M. pruriens* seed produces dose dependent protection against superoxide generation, hydroxyl radical production and $FeSO_4$-induced lipid peroxidation only in *in-vitro*. However, *in-vivo* studies on albino rats, treatment with *M. pruriens* for 30 days did neither show any toxic effect up to a dose of 600-mg/kg p.o. body weight nor changed in the level of TBA-reactive substances, reduced glutathione content and SOD activity in the liver. L-dopa was reported to decrease free radical generation in various *in-vitro* models for radical scavenging activity [28]. L-dopa has been reported to up-regulate glutathione and protect mesencephalic cell cultures against oxidative stress [29]. Pergolide mesylate, a dopaminergic agonist, administered with L-dopa enhances serum antioxidant enzymes in Parkinson disease [30]. Thus, the reduction in lipid peroxidation and increase antioxidant parameters by *M. pruriens* observed in our study may be due to the presence of L-dopa in the extract, acting through dopaminergic mechanism.

In conclusion, our data suggest that *M. pruriens* extract has protective potential against gentamicin-induced nephrotoxicity and oxidative stress in rats. The mechanism may be attributed due to presence of L-dopa in the extract acting through dopaminergic mechanism.

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