

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 dosedependent 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, 5hydroxytryptamine (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 CHCl₃ 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°C) 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 nbutanol: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 $25 \pm 2^{\circ}$ 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 μ g/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 ($22 \pm 2^{\circ}$ C), humidity ($55 \pm 5\%$) 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 \pm 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, further 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.
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Fable 1. Effects of aqueous extract of <i>M. pruriens</i> on various parameters in gentannen induced nephrotoxicity in fats.							
Parameters	Control	MP	GEN	GEN +MP	GEN +MP		
		400 mg/kg		200 mg/kg	400 mg/kg		
Body weight (g)	234 ± 9.78	232 ± 10.06	$196 \pm 4.57*$	207 ± 9.80	213 ± 9.01		
Urine volume (ml/12h)	3.54 ± 0.41	3.82 ± 0.50	$15.32 \pm 1.46*$	19.96 ± 1.57	26.56 ± 2.14**		
Urinary sodium (mg/ml/12hr)	4.08 ± 0.39	4.24 ± 0.29	$2.01\pm0.41*$	2.56 ± 0.40	$3.68 \pm 0.47 **$		
Urea (mg/dl)	36.49 ± 2.21	37.15 ± 3.36	$62.74 \pm 5.43*$	46.30 ± 3.04 **	$41.95 \pm 2.80 **$		
Creatinine (mg/dl)	0.90 ± 0.06	0.89 ± 0.05	$1.77 \pm 0.09*$	$1.26 \pm 0.06 **$	$1.07 \pm 0.07 **$		
Creatinine clearance (ml/min)	0.56 ± 0.02	0.60 ± 0.04	$0.24\pm0.02*$	$0.39 \pm 0.03 **$	$0.53 \pm 0.03 **$		

Each value is mean \pm 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 ne-phrotoxicity 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	$6.01\pm0.40*$	$4.15 \pm 0.41 **$	2.92 ± 0.39**
Superoxide dismutase (U/min/mg of protein)	0.55 ± 0.06	0.54 ± 0.06	$0.22\pm0.03*$	$0.39 \pm 0.03 **$	0.49± 0.04**
Catalase (U/mg of protein)	18.99 ± 2.05	19.57 ± 1.95	$8.96 \pm 1.01 *$	14.72 ± 1.52**	19.49 ± 1.85**
Glutathione (µ mole/ mg of protein)	1.30 ± 0.14	1.32 ± 0.18	$0.30\pm0.07*$	$0.89 \pm 0.09 **$	$1.22 \pm 0.11 **$

Each value is mean \pm 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 STZdiabetic 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]. D₁-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. Irongenatmicin 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 H₂O₂ 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 H₂O₂ 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 H₂O₂ 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-

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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 FeSO₄-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 600mg/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.

REFERENCES

- Ali BH. Gentamicin nephrotoxicity in humans and animals: some recent research. Gen Pharmacol 1995, 26: 1477-1487.
- Cuzzocrea S, Mazzon E, Dugo L, Serraino I, Di Paola R, Britti D, De Sarro A, Pierpaoli S, Caputi A, Masini E, Salvemini D. A role for superoxide in gentamicin-mediated nephropathy in rats. Eur J Pharmacol 2002, 450: 67-76.
- Eisenberg JM, Koffer H, Glick HA, Connell ML, Loss LE, Talbot GH, Shusterman NH, Strom BL. What is the cost of nephrotoxicity associated with aminoglycosides? Ann Intern Med 1987, 107: 900-909.
- Wiland P, Szechcinski J. Proximal tubule damage in patients treated with gentamicin or amikacin. Pol J Pharmacol 2003, 55: 631-637.
- Baliga R, Ueda N, Walker PD, Shah SV. Oxidant mechanisms in toxic acute renal failure. Drug Metab Rev 1999, 31: 971-997.
- Parlakpinar H, Tasdemir S, Polat A, Bay-Karabulut A, Vardi N, Ucar M, Acet A. Protective role of caffeic acid phenethyl ester (cape) on gentamicin-induced acute renal toxicity in rats. Toxicology 2005, 207: 169-177.
- Priuska EM, Schacht J. Formation of free radicals by gentamicin and iron and evidence for an iron/gentamicin complex. Biochem Pharmacol 1995, 50: 1749-1752.
- Pandey GS, Chunekar KC. Bhavprakash nighantu Chaukhamba vidhyabavan, Varanasi. 1996, 357-359.
- Pant MC, Joshi LD. Identification of pharmacologically active substances in the seeds of Mucuna pruriens DC. Ind J Pharmacol 1970, 2: 24-29.
- Mehta JC, Majumdar DN. Indian Medicinal Plants-V. Mucuna pruriens bark (N.O.: Papilionaceae). Ind J Pharm 1994, 6: 92-94.

- Tripathi YB, Upadhyay AK. Effect of alcohol extract of the seeds of Mucuna pruriens on free radicals and oxidative stress in albino rats. Phytother Res 2002, 16: 534-538.
- Grover JK, Vats V, Rathi SS, Dawar R. Traditional Indian antidiabetic plants attenuate progression of renal damage in streptozotocin induced diabetic mice. J Ethnopharmacol 2001, 76: 233-238.
- Carranza A, Karabatas L, Barontine M, Armando I. Decreased tubular uptake of L-3,4- dihydroxyphenyalanine in streptozotocin –induced diabetic rats. Horm Res 2001, 55: 282-287.
- Segers O, Dupont AG, Gerlo E, Somers G. Urinary sodium and dopamine ecretin: role of hyperinsulinaemia in renal dopamine production. Med Sci Res 1996, 24: 571-572.
- Ohkawa H, Ohishi N, Yagi K. Assay for lipid peroxides in animal tissues by thiobarbituric acid reaction. Anal Biochem. 1979, 95: 351-358.
- Mishra H, Frodvich I. The role of superoxide anion in the autooxidation of epinephrine and a simple assay for superoxide dismutase. J Biol Chem 1972, 247: 3170.
- Aebi H. Catalase. In: Bergmeyer, H.U. (Ed.), Methods in Enzymatic Analysis. Academic Press, New York, 1983, pp. 276-286.
- Beutler E. Red cell metabolism. In: A Manual of Biochemical Methods. Grune Strottan, New York, 1975, pp. 67–69.
- Lowry O, Rosenbrough N, Farr A. Protein measurement with the Fiolin-Phenol reagent. J Biol Chem 1951, 193: 265.
- Umrani DN, Goyal RK. Beneficial effects of fenoldopam treatment on renal functions in streptozotocin induced diabetic rats. Clin Exper Hypertens 2002, 24: 207-219.
- 21. Jaiswal SB. Creatinine clearance method. Excretion of drugs: Biopharmaceutics and Pharmacokinetics 1995, 191.
- Abdel-Naim AB, Abdel-Wahab MH, Attia FF. Protective effects of Vitamin E and probucol against gentamicin-induced nephrotoxicity in rats. Pharmacol Res 1999, 40: 183-187.
- Maldonado PD, Barrera D, Medina-Campos ON, Hernandez-Pando R, Ibarra-Rubio ME, Pedraza-Chaverri J. Aged garlic extract attenuates gentamicin-induced renal damage and oxidative stress in rats. Life Sci 2003, 73: 2543-2556.
- Barthelmebs M, Velly J, Grima M, Imbs JL. L-dopa and streptozotocin-induced diabetic nephropathy in rats. Am J Hyperten 1990, 3: 72S-74S.
- Jose PA, Raymond JR, Bated MD, Aperia A, Felder RA, Carey RM. The renal dopamine receptors. J Am Soc Nephrol 1992, 2: 1265-1278.
- Atessahin A, Yilmaz S, Karahan I, Ceribasi AO, Karaoglu A. Effects of lycopene against cisplatin-induce nephrotoxicity and oxidative stress in rats. Toxicology 2005, 212: 116-123.
- Erdem A, Gundogan NU, Usubutuan A. The protective effect of taurine against gentamicin-induced acute tubular necrosis in rats. Nephrol Dial Transplant 2000, 15: 1175-1182.
- Gulcin I. Comparison in vitro antioxidant and antiradical activities of L-tyrosine and L-dopa. Amino Acids 2007, 32: 431-438.
- Han SK, Mytilineou C, Cohen G. L-dopa up-regulates glutathione and protects mesencephalic cultures against oxidative stress. J Neurochem 1996, 66: 501-510.
- Chalimoniuk M, Stepień A, Strosznajder JB. Pergolide mesylate, a dopaminergic receptor agonist, applied with L-dopa enhances serum antioxidant enzyme activity in Parkinson disease. Clin Neuropharmacol 2004, 27: 223-229.

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