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Effect of *Cymbopogon schoenanthus* L. Spreng Extract on Gentamicin-Induced Renal Toxicity in Rats

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Abstract

This study's objective is to assess phytochemicals content and the protective effect of *Cymbopogon schoenanthus* hydro-ethanolic extract on gentamicin-induced renal toxicity in rats. Phytoconstituents were determined by using colorimetric tests. Three methods were used for the evaluation of antioxidant activity. The experiment used gentamicin in six different groups of albino rats. The biochemical analysis of current results displayed a significant reduction in blood urea and creatinine in groups intoxicated with gentamicin and administered two doses of the extract. While the concentration of total proteins and albumins has been increased. In addition, this plant decreased oxidative stress which was translated into a decrease in malondialdehyde content, and increased levels of antioxidant parameters, consequently an improvement in kidney functions. This study revealed a higher content of phenolic compounds, greater antioxidant activity and nephroprotective qualities of *Cymbopogon shoenanthus* extract for the first time.

Keywords: *Cymbopogon schoenanthus*, Gentamicin, Nephroprotective Activity, Poaceae, Polyphenols

1. Introduction

Cymbopogon schoenanthus Spreng, commonly named Lammad, Sounboul el Arabe and Lemongrass[1,2]. Teberimt and Teberint in Tamahaq 1 is an aromatic plant from the Poaceae family[2,3]. It grows wildly in the tropical region through North Africa, Assia[4]. It is well represented in Algeria Sahara[5,6]. It's a perennial grass that creates dense tussocks at the base of many erect 60 cm stems. The leaves are linear, hard and strongly curved[3,7]. The inflorescence contracts at the base, loosens towards the end and is protected by a distinctive spathe[8]. It was found on gravely sandy soil in sand beds with no saline wadi and gravelly stone soils[2,8]. According to reports, this plant provides insecticidal and mosquito-repelling properties against a variety of insects and beetles[9]. As was previously reported, the herb was utilized in the Hoggar region (Sahara of Algeria) to treat rheumatism, renal ailments, and digestive disorders including food poisoning[1,10]. This plant is also used to treat fever and dromedary wounds in the south of Tunisia 6. Previous studies have illustrated the antioxidant and antimicrobial activities of *Cymbopogon schoenanthus* from Algeria Sahara; Illizi, Bechar and Ghardaia[3,11,12]. The antibacterial effectiveness of this species against ovine

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trichostrongylus has been investigated[13]. As a result of its protective effects against different pollutants and renal toxicity drugs, such as gentamicin, more attention has been paid to medicinal plants and herbs[14]. Gentamicin may lead to kidney damage[15] by producing Reactive Oxygen Species (ROS)[16]. Because of its high circulatory contribution (about 20% of cardiac output) and ability to absorb and concentrate extremely dangerous compounds, the kidney is frequently targeted for poisonous xenobiotics. According to experimental data, drug-induced nephrotoxicity may involve vascular, glomerular, and tubular targets due to mechanisms that impair normal cellular structures and functions (such as mitochondria, membrane integrity, etc.), cause renal injury by way of intratubular obstruction (crystal deposition), and encourage cellular swelling and tubular luminal occlusion (via osmotic effects)[15]. The purpose of this study was to investigate the chemical content, antioxidant potential and nephroprotective effects of hydro-ethanolic extract of lemongrass from Hoggar.

2. Material and Methods

2.1 Plant Collection and Preparation of Extract

The aerial part of *Cymbopogon schoenanthus* was collected from Tamanrasset (Coordinates: 22° 48′13″N, 05° 36′57,6″E) in Spring then air-dried at room temperature in the shade. Before analysis, samples were ground to a fine powder using a domestic blunder and used for the preparation of hydro-ethanolic extract.

Further, the plant powder from (10g) was subjected to extraction with ethanol (70%) according to Ye *et al*[17]. A vacuum rotary evaporator was used to evaporate the hydro-ethanolic extract (Büchi Rotavapor R- 200).

2.2 Determination of Phenolic Content

Three different colorimetric methods were used for the estimation of the phytochemical compounds in the hydro-ethanolic extract. The phenolic content was measured with the colorimetric Folin-Ciocalteu method[18]. The reaction was set up by combining 200 ml of extract (1 mg/ml) with 5 ml of ten-fold-diluted Folin-Ciocalteu reagent and then adding 4 ml (75 g/l) of sodium carbonate (three replications). After shaking, the mixture was left to stand at room temperature for 30 min. The Shimadzu UV-VIS-1240 spectrophotometer was used to measure optical density at 765 nm. The quantity of total phenolic compounds was calculated as µg gallic acid equivalent/mg of plant extract.

2.3 Measurement of the Total Flavonoid

Spectrophotometry methods have been used to determine the flavonoid content of hydro-ethanolic extract[19]. In this procedure, a 0.5 ml aliquot of the sample was incorporated with 0.5 ml of a 2% $AlCl_3$ methanol solution. After an hour at ambient temperature, the mixture's absorbance at 420 nm was established. To create the calibration curve, rutin was employed as a standard. Three separate measurements of the total flavonoids in the extract were measured, and the results were averaged.

2.4 Concentration of Condensed Tannin

According to the vanillin/HCl assay 20 technique, condensed tannin was assessed. About 50 mL of extract, 3 ml of methanol-vanillin solution, and 2.5 mL of HCl were put into sample tubes, which were left at ambient temperature for 20 min[20]. The absorbance was measured at 500 nm and results were expressed as µg catechin equivalents per mg of extract.

2.5 Antioxidant Capacity Assessment using the Phosphomolybdenum (PM) Technique

The method developed by Ramu *et al*.,[21] assessed the total antioxidant capacity of hydro-ethanolic extract of lemongrass with little modifications. In brief, 1 mL of integrating chemical mixture (0.6 M sulphuric acid, 30 mM sodium phosphate, and 4 mM ammonium molybdate) was added to 0.1 mL of extract. In a boiling water bath at 95°C for 90 min, the sample tubes were sealed and incubated. The reactant specimens were cooled to room temperature following incubation and their absorbance against the blank was measured at 695 nm (containing the same reagent without sample). The equation obtained from the calibration curve for ascorbic acid has been used to calculate antioxidant activity as µg of ascorbic acid Equivalent.

2.6 FRAP Assay: Ferric Reducing Antioxidant Capacity

This approach is based on an antioxidant's ability to decrease Fe^{+3} to Fe^{+2} in the presence of triazine (2,4,6-tris (2-pyridyl)-s). A mixture of 0.3 M acetate buffer (pH 3.6), 10 mmol TPTZ solution in 40 mmol HCl, and 20 mmol iron (III) chloride solution were combined

in the following ratios: 10:1:1 (v/v), and 0.3 mL of sample (0.1 mg/mL) was then added. This created an aliquot of 2.7 ml of FRAP reagent. Ascorbic acid equivalents per g of plant extract are used to express the results[22].

2.7 Diphenyl-1-Picrylhydrazyl (DPPH) Radical Scavenging Activity

The radical scavenging activity of the stable DPPH free radical was used to assess the antioxidant properties of the plant extract[23]. Employing methanol, 100 µM of DPPH solution was created. 100 µL of sample and 2 mL of the DPPH solution were combined in test tubes and incubated for 30 min at room temperature, outside light, and the absorbance was measured at 517 nm. Methanol was used as a blank to measure the solution alone before the addition of the samples. A plot of inhibition percentage versus extract concentration has been obtained for the extract concentration providing 50% inhibition (IC50).

2.8 Animals and Experimental Design

Animal experiments used for this study were obtained from the Institute of Pasteur in Algeria. Twenty-four adult female *Wistar* rats weighing between 203g and 269g were allowed in a plastic cage at room temperature (18±1 °C), humidity (65%) and a 12 h dark-light cycle in the laboratory of the Faculty of Nature Sciences and Life/ el Oued-University for fifteen days of adaptation with free access to standard foods and physiologic water. The rats were divided into 6 groups as follows: Group 1 consisting of 4 rats received daily physiological water orally for eight days (A). Group 2 received only the hydro-ethanolic extract orally (B). Group 3 received 80 mg/ kg/day of gentamicin i.p (C). Groups 4 and 5 were pre-treated with 100 mg/ kg and 300 mg/kg of hydro-ethanolic extract concurrent to 80 mg/kg of gentamicin i.p. respectively (D; E). Group 6 was pre-treated with vitamin C 200 (F) mg/kg/day in addition to 80mg/kg of gentamicin i.p., respectively. Rats from each group were sacrificed on the 8th day following an overnight fast[24]. Experiments were approved by the Committee of the Association Algérienne des Sciences en Experimentation Animale (http://aasea.asso.dz/articles/) under Law No.8808/1988, associated with veterinary medical activities and the protection of animal health.

2.9 Biochemical Assay

blood was collected from the test animals into dry tubes and centrifuged at 3000 rpm for 15 min for estimation of urea, creatinine, total proteins, albumin and electrolytes) following the protocols provided with the commercial kits and automatic biochemical analysis (BIOLIS24j).

2.10 Indicators of Tissue Oxidative Stress Markers

Sections (1g) from the kidney tissues were homogenized after that the homogenates were centrifuged at 3000×g for 15 min, and the supernatants were used for the estimation of the antioxidant markers Malondialdehyde (MDA), reduced Glutathione (GSH), Glutathione Peroxidase (GPX) and catalase by the methods of Shalabyan and Hamouda[14] and Zariyantey *et al*[25].

2.11 Statistical Analysis

Each experiment was performed three times and was represented as the mean ± SEM using MINITAB17. ANOVA process was adopted for analysis of variance. Statistical comparisons between means were determined by the Student test. P values < 0.05 were considered as significant.

2.12 Histopathological Study

Histological sections of renal tissue were analyzed. After dehydrating in alcohol and depositing the tissues in paraffin, material sections were made using a microtome device. The slides were then stained with hematoxylin-eosin and inspected under a light microscope[26].

3. Results

3.1 Assessing Phytoconstituents

The extract yields 6.85% of an extract with a brown colour and pasty aspect. Quantitative evaluation of phenolic, tannin and flavonoid contents was estimated using colometric methods (Table 1) with values: 29,39 ± 2,20 µg

Table 1. Yield, total phenol, flavonoid and tannin contents of *Cymbopogon shoenanthus* extract

Yield %	Phenolic content µg EGA/E	Flavonoid content µg E Q/mg E	Condensed tannin content µg E C/mg E
6.85±0.54	29,39±2,20	8,84±0,31	3,91±0,14

The phenolic content value was determined as µg equivalent of gallic acid / mg of extract
Flavonoid content value was determined as µg equivalen t of quercitin/ mg of extract
Condensed tannin content value was determined as µg equivalent t of catechin/ mg of extract

AGE/ mgE, 3,91 ± 0,140 µg CE/mg and 8,84 ± 0,31 µgQE/ mgE dry extract, respectively.

3.2 The Antioxidant Activity

As the number of equivalent ascorbic acids, the total antioxidant activity of the extract was calculated. The extract showed a high value of 342,95 ± 0,96µg AAE/mg dried extract for the PM method. However, less activity

Table 2. Antioxidant activity of *Cymbopogon shoenanthus* extract and ascorbic acid

Extract	PM µg AA/ mg E	FRAP µg AA/mg E	DPPH assay IC_{50}(µg/ml)
Hydro-ethanolic	342,95±0,96	81,52±1,35	113,38±3,17
Ascorbic acid	/	/	11,19±1,15

PM and FRAP values were determined asµg equivalent to ascorbic acid/ mg of extract

Table 3. Blood levels of biochemical parameters

Groups	A	B	C	D	E	F
Urea (g/l)	0.48±0.02	$0.50±0.01^{NS}$	2.83±0.06*	$0.53±0.03^{b}$	$0.54±0.03^{b}$	$0.55±0.01^{a}$
Creatinine (mg/l)	8.28±0.49	$9.40±0.43^{NS}$	60.72±2.43**	$10.62±0.72^{b}$	$12.09±1.23^{b}$	$10.81±0.76^{c}$
Proteins(g/l)	79.59±0.41	$78.01±0.83^{NS}$	63.91± 0.97*	$78.84±1.92^{a}$	$76.80±0.80^{b}$	$76.75±0.76^{b}$
Albumin (g/l)	44.83±0.82	$45.44±1.32^{NS}$	31.62±0.62**	$43.11±1.17^{a}$	$43.13±0.88^{a}$	$44.56±0.55^{b}$

Values are given as mean ±SEM. * = Significantly different fromnormal control *p<0.05; **p<0.01; *** p<0.001. a= Significantly different from gentamicin group [a] p<0.05; [b] p<0.01; [c] p<0.001.

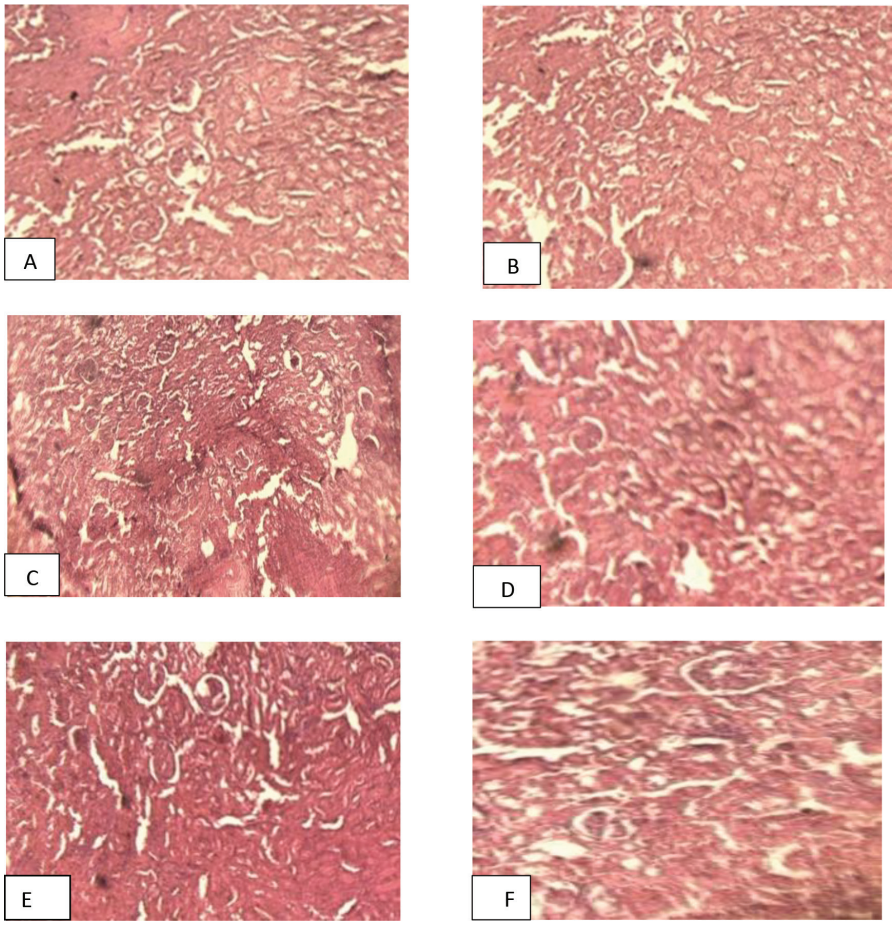


Figure 1. Histopathological structure of normal kidney tissue and after treatment with extract and vitamin. **A** = control group, **B** = extract group, **C** = gentamicin group, **D, E** and **F** = treated groups, respectively at the doses of 100, 300 mg/kg and vitamin C group (HE X 40).

for the FRAP test with 81,52 ± 1,35µg AAE/mg extract was revealed. DPPH radical scavenging activity was determined and the IC_{50} value was found to be 113,38 ± 3,17 µg /ml and 11,19 ± 1,15µg/ml for extract and ascorbic acid respectively (Table 2).

3.3 Analysis of Biochemical and Oxidative Stress Markers

Table 3 revealed that urea and creatinine levels were considerably ($p<0.05$) higher in the C group than in the A group (normal control). However, these quantities were markedly reduced ($p^b<0.01$) and ($p^c<0.001$) in the treated groups D, E and F respectively, Compared with A, the administration of this extract to normal rats B does not affect urea and creatinine levels. Serum total proteins and albumin of the C group were considerably decreased ($p<0.05$) compared to A. However, studies that supplemented the extract with gentamicin in groups D and E showed a markedly elevated content of total proteins and albumin ($p<0.05$) compared to A. Similar results occurred in the F group after receiving vitamin C treatment.

3.4 Histopathological Investigation

The control group A and group administered only extract showed a normal kidney section architecture (Figure 1) followed by kidney sections of groups treated with gentamicin (C), gentamicin and extract (100 and 300 mg/kg), gentamicin with vitamin C, which showed improvement in the structural damage caused by gentamicin (infiltration of lymphocyte).

Table 4. Electrolytes blood levels

Groups	A	B	C	D	E	F
Na^+ (mml/l)	140.18±0.62	137.02±0.67 ^{NS}	132.70±1.43*	138.80±0.49^a	139.90±0.73^a	140.73±0.13^a
K^+ (mml/l)	5.38±0.020	5.33±0.030 ^{NS}	7.04±0.07*	5.14±0.03^a	5.38±0.08^b	5.38±0.08^b
Cl^- (mml/l)	105.70±0.20	103.11±0.67 ^{NS}	102.90±0.40*	106.33±0.65^a	106.26±0.86^a	107.70±0.45^b

Values are given as mean ±SEM. * = Significantly different from normal control *p<0.05; **p<0.01; *** p<0.001. a= Significantly different from gentamicin group ^{a} p<0.05; ^{b} p<0.01; ^{c} p<0.001.

Table 5. Kidney oxidative stress markers analysis

Groups	A	B	C	D	E	F
MDA (µmol/mg tissue)	0.24±0.01	0.23±0.01^{NS}	0.377±0.030*	0.26±0.01^a	0.25±0.02^a	0.27±0.02^a
GSH (nM/mg tissue)	0.26±0.01	0.25±0.01^{NS}	0.088±0.005**	0.22±0.014^a	0.25±0.00^b	0.25±0.00^b
GP_X (µmol /mg prot)	2.37±0.11	2.34±0.15^{NS}	1.024±0.059**	2.24±0.14^b	2.27±0.11^a	2.20±0.19^a
Catalase (UI/mg prot)	108.1±10.30	110.70±4.5^{NS}	31.5±5.70*	67.5±3.50^a	101.91±3.40^a	109.22±9.21^a

Values are given as mean ±SEM. Significantly different from normal control *p<0.05; **p<0.01; *** p<0.001. Significantly different from gentamicin group ^{a} p<0.05; ^{b} p<0.01; ^{c} p<0.001

4. Discussion

In nephrology, the investigation for herbal remedies with antioxidant properties has received attention because of their interest in biological and protective effects[6,27], recently several researchers have focused on polyphenolic compounds and their strong antioxidant capacities[23,28-30]. Compared to previous work the present results were lower than those reported by Chaib *et al.*,[31] with 64,962 ±1,142 mg gallic acid equivalent and 19,354±1,841 µg quercetin equivalent for polyphenols and flavonoid, respectively. The report of Khadri *et al.*,[6] showed higher contents in phenolic, flavonoid and condensed tannin water extract of *Cymbopogon shoenanthus* from different localities in Tunisia particularly the plant harvested in desert or mountain regions. These differences may be attributed to the method used, the extraction methodology and the plant composition and its origin[27].

The potential antioxidant effect and the scavenger activity of the extract may be explained by the potential effect of samples to send electrons or liberate a proton in the reaction[32]. Antioxidant activities of lemongrass located in South Tunisia were also determined using the β-carotene/linoleic acid bleaching test and DPPH assay have displayed good results[33].

The role of gentamicin in inducing nephrotoxicity is shown by many reports including[14,24,34-38]. Gentamicin is an antibiotic but can induce nephrotoxicity[36]. by causing oxidative stress[34,38]. Characterized by significant elevation in blood biochemical parameters such as creatinine and urea[36]. These latter were used as a marker of man's and animals' nephrotoxicity[38]. The co-administration of extract and gentamicin to rats for eight days consecutively has restored significantly these biochemical parameters to normal levels as the control group these most recent findings correlate with other sources including Raju *et al.*,[24] and Kuatsienu *et al*[36]. Because of no balance in glomerular function by reducing their filtration rate and renal blood flow[35,37].

Furthermore, the present study revealed that there is a variation in kidney electrolyte levels in the C group which revealed a significant decrease ($p<0.05$) of Na^+ and Cl^- concentrations in comparison to the NC, but these electrolyte levels in groups co-administered the extract or vitamin C with the gentamicin were significantly ($p<0.05$) elevated to normal levels when compared to gentamicin group. Serum concentration values of K^+ were contrary to Na^+ and Cl^- levels in all the groups. However, this is not in agreement with the report of reference[36] (Table 4).

Oxidant stress markers such as the lipid peroxidation markers MDA in the kidney were significantly increased in the C group demonstrating that gentamicin toxicity was responsible for ROS generation and kidney damages[39], nevertheless the animals received extract at 100mg/kg and 300mg/kg concurrent with gentamicin decreased significantly the concentration of MDA compared to C group ($p<0.05$). Observed in the F group, MDA levels were significantly reduced compared to the C group ($p<0.05$). In addition, the GSH levels in this latter were decreased significantly when compared to normal control, although the administration of extract and vitamin C concomitantly with gentamicin elevated significantly the concentration of GSH. Catalase (CAT) and Glutathione Peroxidase (GPx) enzyme activity was significantly elevated in kidney tissues ($p<0.05$) when administered the extract along with gentamicin which was attributed to its content in antioxidant constituents[14]. This data is from the recent studies of Sharma *et al.*,[39] but this activity was significantly decreased ($p<0.05$) in the C group when compared to normal rats. However, the extract showed more efficacy at a dose of 300 mg/kg (Table 5). Pathological changes were noticeably increased in the kidney tubules of gentamicin-administered rats, as clearly explained in a histological analysis. Furthermore, in this investigation treatment with *Cymbopogon shoenanthus* extracts significantly reduced the amount of leukocyte accumulation in the kidneys of the rats, confirming that this species exhibits protective effects on kidney tissues. To the best of my knowledge, this is the first report to reveal the protective activity of *Cymbopogon shoenanthus* hydro-ethanolic extract on gentamicin-induced nephrotoxicity.

5. Conclusion

This important investigation shows the chemical content of *Cymbopogon shoenanthus* hydro-ethanolic extract and its higher antioxidant potential activity *in vitro.* Additionally, the remarkable recovery of biochemical markers for renal function and the improvement of antioxidant enzymes in rats treated with toxic substances allowed for the evaluation of its nephroprotective action in gentamicin-intoxicated animals.

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