

Haemato-biochemical Effects of Aqueous Extract of *Khaya senegalensis* Stem Bark on Gentamicin-Induced Nephrotoxicity in Wistar Rats

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Abstract: The haemato-biochemical effects of aqueous extract of *Khaya senegalensis* were tested against gentamicin induced nephrotoxicity in Wistar rats. Rats were divided into 6 groups of 5 rats each. All rats were treated orally for 8 days. Rats in group 1 served as control group and received distilled water at 2 mL kg⁻¹/day, group 2 received distilled water at 2 mL kg⁻¹ and received gentamicin 100 mg kg⁻¹ intramuscularly for the last 5 days, groups 3 and 4 received the aqueous extract of *K. senegalensis* stem bark orally at 500 and 250 mg kg⁻¹, respectively and on the last 5 days they received gentamicin at 100 mg kg⁻¹ intramuscularly. Groups 5 and 6 received the aqueous extract of *K. senegalensis* alone at 500 and 250 mg kg⁻¹, respectively. Red Blood Cell (RBC) count, Haemoglobin (Hb), Haematocrit (PCV), Mean Corpuscular Volume (MCV) and Mean Corpuscular Hemoglobin Concentration (MCHC) were determined. Measurement of urea, creatinine, total protein and albumin were investigated. The kidney tissues were microscopically examined. Intramuscular administration of gentamicin to rats resulted in significant elevation of serum urea, creatinine, total protein and albumin with massive tubular necrosis and degeneration of renal cortical tubules. Oral administration of *Khaya senegalensis* at 250 and 500 mg kg⁻¹ to rats significantly ameliorated the increase in serum urea, creatinine, total protein and albumin and similarly ameliorate the damage in the kidney tubules. This study suggested nephroprotective effect of *Khaya senegalensis* aqueous extract which may be due to antioxidant properties of the extract together with the phytochemical constituents of *K. senegalensis*.

Key words: Antioxidant, nephroprotective, *Khaya senegalensis*, Wistar rats

INTRODUCTION

Gentamicin is commonly used aminoglycoside antibiotic but nephrotoxicity are the most common adverse reactions (Martinez-Salgado *et al.*, 2007; Rybak and Ramkumar, 2007). Aminoglycoside nephrotoxicity is characterized by decreased urine concentration capacity, tubular proteinuria, mild glucosuria, decreased ammonium excretion and lowering of glomerular filtration rate (Kaloyanides and Pastoriza-Munoz, 1980). *In vitro* studies have demonstrated that aminoglycoside enhances phospholipid membrane peroxidation (Walker and Shah, 1987) and Ramasammy *et al.* (1986) reported that there is an increase in renal cortical lipid peroxidation in gentamicin treated rats.

Khaya senegalensis belongs to the family Meliaceae (Mahogany family) and used traditionally in Sudan to

treat Malaria. The liquid preparation obtained by boiling medicinal plant in water and extracting drugs by straining the preparation is given as remedy for malaria and also been used as an anthelmintic, emetics, emmenagogue and in treatment of jaundice (Gill, 1992). Sami *et al.* (2005) reported that, oral administration of aqueous extract of stem bark of *K. senegalensis* to rats at 300 mg kg⁻¹ produced significant antianemic activity. Nwosu *et al.* (2012) reported that the aqueous and methanolic extracts of *K. senegalensis* have anti-diarrhoeal activity and the aqueous extract of the plant was more effective than methanolic extract. The toxicity studies did not reveal any apparently harmful or deleterious effect of leaves of *K. senegalensis*. Lompo *et al.* (2007) found in their study that the aqueous and ethanolic crude extracts and fractions of *Khaya senegalensis* stem barks are able to scavenge significantly free radicals of DPPH. Fractions can play a pivotal role in the antioxidant activity of crude

lyophilised aqueous and alcoholic extract of stem barks of *Khaya senegalensis*. Thioune *et al.* (1999) investigated some anti-inflammatory tests out with a freeze-dried aqueous extract and an etheropetrolic extract of *Khaya senegalensis* barks. Their results have shown a decrease of the oedema. Aqueous extract of *K. senegalensis* reported by Ali *et al.* (2011), possesses hepatoprotective activity against CCl₄ hepatotoxicity.

The present study was planned to examine the haemato-biochemical effects of aqueous extract of stem bark of *K. senegalensis* on gentamicin- induced nephrotoxicity in Wistar rat.

MATERIALS AND METHODS

This study was conducted in the Faculty of Veterinary Medicine University of Khartoum Sudan (2011-2012).

Preparation of the plant extract: *K. senegalensis* bark were collected from El Dmazin, Blue Nile State-Sudan and authenticated by Botanist in the Medicinal Plant Institute-National Research Centre, Khartoum-Sudan. Fresh barks of the plant were collected and were shade dried and then made into powder; the powder of the bark was soaked in boiling distilled water and left for two hours at room temperature. The mixture was filtered. The filtrate was cooled over night at 4°C (Sanni *et al.*, 2005; Adakole and Balogun, 2011).

Experimental animals: Thirty six Wistar, Male and female adult albino rats weighing 160-180 g were used in the this experiment and were obtained from the Medicinal and Aromatic Plants Research Institute, Khartoum, Sudan and reared within the premises of the Institute, under illumination at night and early morning with feed and water provided *ad libitum*.

All experiments conform to guidelines governing the handling of laboratory animals as laid out by the Faculty of Veterinary Medicine, University of Khartoum Committee on Ethics for Scientific and Medical Research.

Nephroprotective activity: Rats were divided into 6 groups of 5 rats each. Rats in group (1) served as control group and received distilled water at 2 mL kg⁻¹/day, orally, for 8 days, group (2) received distilled water at 2 mL kg⁻¹ orally for 8 days and received gentamicin 100 mg kg⁻¹ intramuscularly for the last 5 days, groups 3 and 4 received the aqueous extract of *K. senegalensis* stem bark orally at 500 and 250 mg kg⁻¹, respectively for 8 days and on the last

5 days they received gentamicin at 100 mg kg⁻¹ intramuscularly. Groups 5 and 6 received the aqueous extract of *K. senegalensis* alone at 500 and 250 mg kg⁻¹, respectively for 8 days orally.

Antioxidant activity: (a) DPPH radical scavenging assay; The DPPH radical scavenging was determined according to the method of Shaheen *et al.* (2005) with some modification. In 96-wells plate, the test samples were allowed to react with 2,2-Di(4-tert-octylphenyl)-1-picrylhydrazyl stable free radical (DPPH) for half an hour at 37°C. The concentration of DPPH was kept as (300 µM). The test samples were dissolved in DMSO while DPPH was prepared in ethanol. After incubation, decrease in absorbance was measured at 517 nm using multiplate reader spectrophotometer. Percentage radical scavenging activity by samples was determined in comparison with a DMSO treated control group. All tests and analysis were run in triplicate.

Biochemical analysis: At the end of the experimental period blood was taken from ocular pluxes for serum analysis which include measurement of urea, creatinine, total protein and albumin using commercial kits (Biosystem S.A Costa Brava 30, Barcelona Spain).

Haematological analysis: Red Blood Cell (RBC) count, Haemoglobin (Hb), Haematocrit (PCV), Mean Corpuscular Volume(MCV) and Mean Corpuscular Hemoglobin Concentration (MCHC) were recorded by using haematological auto-analyzer (Huma-plus).

Histopathological analysis: The kidney tissues were dissected out and fixed in 10% formalin. Sections were prepared and then stained with hematoxylin and eosin (H and E) dye and then examined microscopically.

Statistical analysis: The data are expressed as Mean±SEM the difference among means has been analyzed by one-way Analysis of Variance (ANOVA) (SPSS version 16). A value of p<0.05 was considered as statistically significant.

RESULTS

In vitro antioxidant activity of *Khaya senegalensis*:
DPPH scavenging activity: Table 1 Indicate that, the water extract of *K. senegalensis* has a dose dependent activity which was increased with increasing concentration and the IC₅₀ of the extract was found to be

102 µg mL⁻¹. RSA% (Radical scavenging activity) of the aqueous extract of *K. senegalensis* was found to be 66.6% which is better than the RSA of the standard propyl gallate which is 64.85%.

Biochemical results: The effect of *K. senegalensis* aqueous extract on serum urea, creatinine, total protein and albumin are presented in Table 2. The gentamicin group 2 scored the higher values of urea, creatinine and total protein when compared to the normal control and when compared to the treated groups. *K. senegalensis* at 500 and 250 mg kg⁻¹ significantly lowered the values of urea, creatinine and total protein and significantly increased the concentration of albumin; the lower dose seems to be better in protecting the kidney from gentamicin damage.

Haematological results: Haematological parameters are presented in Table 3. In gentamicin treated rats the values of RBC, Hb and PCV were significantly lower than the values of these parameters in the control group and values of MCV and MCHC were significantly lower when compared to the control, the extract of *K. senegalensis* significantly increased the values of RBC, Hb and PCV in

groups 3 and 4 that treated with 500 and 250 mg kg⁻¹ of the extract. The values of Hb, RBC and PCV in rats treated with the extract alone showed normal values of these parameters when compared to the control group while the values of MCV and MCHC were significantly lower than the gentamicin treated group.

Histopathological results: Histopathological findings of *K. senegalensis* treated rats on gentamicin induced kidney damage are presented in Fig. 1a-d. Figure 1a showed kidney sections of rats treated with gentamicin showing necrosis of tubular cells with renal casts and glomerular congestion, Fig. 1b showed kidney sections of rats treated with 500 mg kg⁻¹ of *K. senegalensis* showed slight necrosis and renal casts. (c) kidney sections of rats treated with 250 mg kg⁻¹ of *K. senegalensis* showing almost intact glomeruli. (d) kidney section of rats administered with *K. senegalensis* alone at 250 mg kg⁻¹ showing almost normal architecture.

DISCUSSION

The results of the present study indicate that the aqueous extract of *Khaya senegalensis* possesses nephroprotective ingredients. The elevation of serum urea, creatinine, total protein and albumin on gentamicin treated rats indicate kidney damage, the decreased concentration of these parameters in the extract treated rats at 250 and 500 mg kg⁻¹ indicates protection of the kidney. The dose 250 mg kg⁻¹ manifest higher protection than 500 mg kg⁻¹, the higher dose may caused adverse effect, although it showed slight protection and this was in line with the results obtained by Kolawole *et al.* (2011), who reported adverse effect to vital organs on prolonged administration of aqueous extract of *K. senegalensis* to rats at 100 and 200 mg kg⁻¹ for 21 days.

The nephroprotective effect revealed by the lower dose 250 mg kg⁻¹ may be due to antioxidant activity of the extract obtained in this study which is 64% on DPPH scavenging activity and IC₅₀ of 120.

The administration of aqueous extract of *K. senegalensis* alone to rats at 250 and 500 mg kg⁻¹ for 8 days showed no adverse effect. The concentration of urea, creatinine, total protein and albumin showed no significant alteration from the normal control and this

Table 1: DPPH scavenging activity of aqueous extract of *K. senegalensis*

Conc. (µg mL ⁻¹)	RSA (%)		
	<i>K. senegalensis</i>	Propyl gallate (Standard)	IC ₅₀
500	66.60±0.008	64.85±0.021	102.00±7.00
250	63.09±0.007	60.75±0.006	
125	53.98±0.006	53.46±0.013	
60.25	45.28±0.005	46.18±0.014	

Values are Mean±SEM, RSA: Radical scavenging activity

Table 2: Effects of *Khaya senegalensis* (Ks) on biochemical parameters of rats intoxicated with gentamicin

Parameters	Urea (mg kg ⁻¹)	Creatinine (mg kg ⁻¹)	Total protein (g dL ⁻¹)	Albumin (g dL ⁻¹)
Control	30.00±1.37	0.54±0.12	6.5±1.03	4.60±0.12
Gm	132.00±13.12**	1.60±0.05**	8.6±1.01**	3.70±0.82**
Gm+500 Ks	108.00±9.32*	0.76±0.06*	7.0±1.25	4.50±0.71*
Gm+250 Ks	53.00±7.72*	0.51±0.07*	7.9±1.16*	4.11±0.35*
500 Ks	39.01±3.52*	0.62±0.04*	8.4±1.15	3.50±0.62
250 Ks	25.02±1.37*	0.54±0.12*	6.5±1.03*	4.60±0.13*

Values are Mean±SEM, **Significant at p<0.05 when compared to normal group, *Significant at p<0.05 when compared to gentamicin group
Gm: Gentamicin

Table 3: Haematological findings of rats treated with *K. senegalensis* (Ks) on gentamicin intoxicated rats

Parameters	RBC (10 ⁶ ×Ml)	Hb (g dL ⁻¹)	PCV (%)	MCV (fl)	MCHC (%)
Control	7.20±0.52	13.21±0.29	41.63±1.21	57.52±1.37	31.70±0.21
Gm	9.98±0.62**	11.4±0.51**	35.40±1.2**	59.20±1.35**	32.20±0.32**
Gm+500 Ks	6.48±0.53*	11.69±0.43	35.70±1.34	59.32±1.53	32.50±0.37
Gm+250 Ks	8.56±0.61*	14.70±0.33*	49.21±1.17*	57.50±2.01*	29.90±0.19*
500 Ks	7.9±0.35*	13.80±0.51*	46.72±1.255*	59.1±1.17	29.61±0.25*
250 Ks	7.00±0.71*	14.21±0.40*	45.31±1.19*	56.30±1.09*	30.30±0.37*

Values are Mean±SEM, **Significant at p<0.05 when compared to normal group, *Significant at p<0.05 when compared to gentamicin group,
Gm: Gentamicin

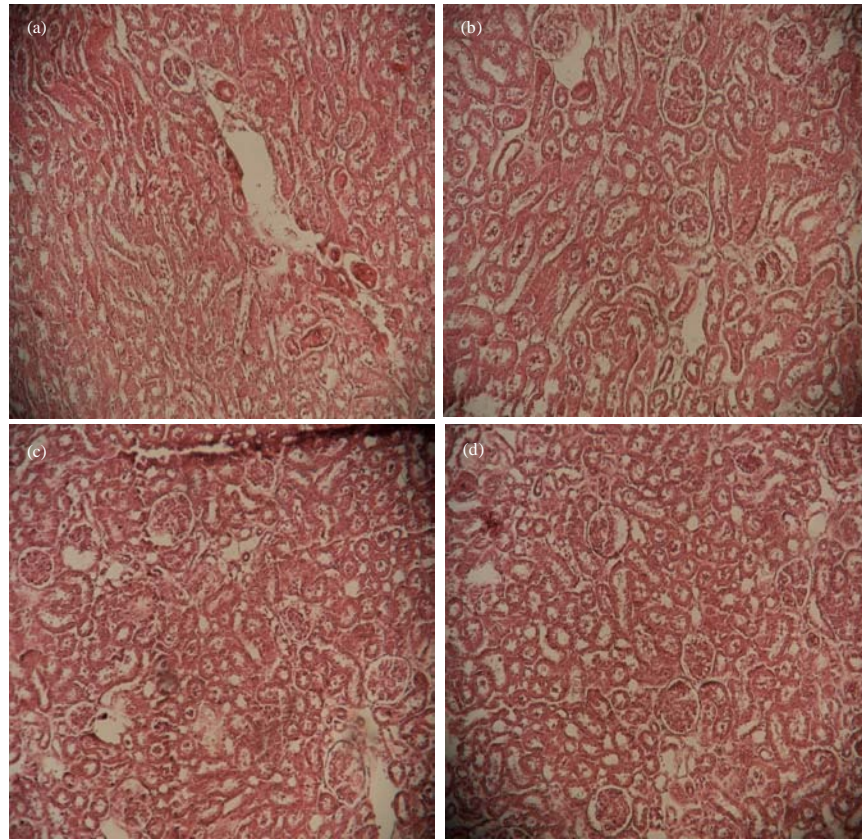


Fig. 1(a-d): Kidney sections of rats treated by *Khaya senegalensis* on gentamicin-induced kidney damage, (a) Necrosis of tubular cells with renal casts and glomeruli congestion, (b) 500 mg kg⁻¹ of *K. senegalensis*, slight necrosis and renal casts, (c) 250 mg kg⁻¹ of *K. senegalensis*, almost intact glomeruli (d) *K. senegalensis* alone at 250 mg kg⁻¹, almost normal architecture

again was in line with the study of Adebayo *et al.* (2003) who reported that no adverse effect of aqueous extract of *K. senegalensis* for 6 days but he observed adverse effect on prolonged administration for 18 days, consequently we reported that, the administration of the extract at higher dose 500 mg kg⁻¹ for 8 days dose not produced adverse effect but failed to protect the gentamicin damage as that obtained by 250 mg kg⁻¹. Protection of the kidney from gentamicin toxicity by medicinal plants was well documented; Lakshmi and Sudhakar (2010) reported that, administration of *Zingiber officinale* at 200 mg kg⁻¹ to rats, produced nephroprotective effect and same protection reported by Abdelaziz and Kandeel (2011) when administrated *Nigella sativa* oil and *Allium sativum* extract on Amikacin induced nephrotoxicity in rats. Ige *et al.* (2011) reported that, Co-treatment with *Allium cepa* during cadmium administration showed significant antioxidative potentials in preventing cadmium induced

nephrotoxicity in rats. Al-Attar (2011) reported nephroprotective effect of *Avicennia alba* in rats treated with ethanol.

Co-administration of water soluble *Rheum emodi* with gentamicin prevented the rise in blood urea and serum creatinine (Alam *et al.*, 2005).

Ginkgo biloba extract protected rats from gentamicin-induced nephrotoxicity. Changes in blood urea, serum creatinine and creatinine clearance induced by gentamicin were significantly prevented by Ginkgo biloba extract (Naidu *et al.*, 2000).

In this study, the nephroprotection produced by *K. senegalensis* was confirmed histopathologically by the decreased damage appeared in the kidney tubules of treated rats which revealed recovery of many tubules from the nephrotoxic effect produced by gentamicin and this was in line with the results obtained by Abdin *et al.* (2008) who reported amelioration in the nephrotoxic effect of

Cisplatin by N- acetylcysteine and also with the results of Adeneye and Benebo (2008) when treated rats with *Phyllanthus amarus* on gentamicin intoxicated rats, same results were obtained by Abdelmeguid *et al.* (2010), who found that, pretreatment with Silymarin before Cisplatin, significantly decreased the histopathological and ultrastructural changes in the kidneys which induced by Cisplatin and Silymarin appear highly protective for the kidneys.

Nephrotoxicity caused by gentamicin caused significant reduction ($p = 0.05$) in levels of Hb, RBC and PCV when compared to the normal control groups. *K. senegalensis* aqueous extract significantly ameliorate the decrease in these parameters which significantly elevate Hb, RBC and PCV values and this result was again better in the lower dose (250 mg kg^{-1}) than the higher dose (500 mg kg^{-1}) while there were no significant changes in MCV or MCHC. In groups treated with the plant alone at 250 and 500 mg kg^{-1} there was significant increase in the level of Hb in the groups treated with 250 mg kg^{-1} and in level of PCV in both groups, these results suggest that the plant contain constituent which can enhance hematopoiesis and this was in line with the result obtained by Adeneye *et al.* (2008) who reported improving haematological status in rats treated with *Harungana madagascariensis* on acetaminophen induced kidney damage in rats.

Shirwaikar *et al.* (2004), Afzal *et al.* (2004) and Ali (2002) reported normalization of serum urea and creatinine on gentamicin model when treated rats with *Aerva lanata* and Jawarish zarooni sada (Polyherbal Unani formulation) and *Rhazya stricta*, respectively.

Nephroprotection due to antioxidant constituent of medicinal plants was proved by many researchers. Annie *et al.* (2005) suggest that nephroprotection by *Cassia auriculata* against Cisplatin and gentamicin induced renal injury could be due to its antioxidant and free radical scavenging properties. Lompo *et al.* (2007) reported that, aqueous and ethanolic extracts and fractions of *Khaya senegalensis* stem bark were able to scavenge significantly free radicals of DPPH (1,1 diphenyl-2-picrylhydrazyl) and these were in line with our results.

CONCLUSION

The results presented in this paper showed that the aqueous extract of *K. senegalensis* showed antinephrotoxic activity which mostly be related to its antioxidant activity and its phytochemical constituents. Further study should be focused on the other extracts of the *K. senegalensis*.

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