EUROPEAN JOURNAL OF BIOMEDICAL AND PHARMACEUTICAL SCIENCES
http://www.ejbps.com

ISSN 2349-8870
Coden USA: EJBPBO
Volume: 13
Issue: 6
Year: 2026

NEPHROPROTECTIVE EFFECT OF HYDROALCOHOLIC LEAF EXTRACT OF *CINNAMON MALABATRUM* AGAINST GENTAMICIN-INDUCED NEPHROTOXICITY IN WISTAR RATS

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DOI: https://doi.org/10.5281/zenodo.20641314

How to cite this Article: P. Akhila[1]*, S. N. V. L. Sirisha[2], S. Tajuddin[1], R. L. Manisha[1]. (2026). Nephroprotective Effect of Hydroalcoholic Leaf Extract of Cinnamon Malabatrum Against Gentamicin-Induced Nephrotoxicity In Wistar Rats. European Journal of Biomedical and Pharmaceutical Sciences, 13(6), 370–378.

Article Received on 21/05/2026 **Article Revised on 05/06/2026** **Article Published on 10/06/2026**

ABSTRACT
Gentamicin is a useful aminoglycoside antibiotic whose clinical value is limited by a tendency to damage the kidney through oxidative injury to the proximal tubule. The leaves of *Cinnamon malabatrum*, an aromatic tree of the Western Ghats, are a rich source of flavonoids, tannins and phenolics. The present study assessed the protective effect of a hydroalcoholic leaf extract of *C. malabatrum* against gentamicin-induced nephrotoxicity in Wistar rats. Authenticated leaf powder was defatted with petroleum ether and re-extracted with ethanol and water (1:1) in a Soxhlet apparatus, giving a yield of 3.68 % w/w. Thirty rats were divided into five groups of six: normal control; disease control receiving gentamicin (100 mg/kg, intraperitoneal, for 7 days); a standard group receiving silymarin (100 mg/kg, oral, for 14 days); and two test groups receiving the extract at 150 and 300 mg/kg orally for 14 days. Gentamicin raised blood urea nitrogen, serum creatinine and renal malondialdehyde and lowered body weight, creatinine clearance, reduced glutathione, urine output and urinary pH. Both doses of the extract reversed these changes in a dose-related way, and the higher dose gave values close to those of silymarin. Renal histology, badly disturbed by gentamicin, was largely preserved in the treated groups. The findings show that the leaf extract of *C. malabatrum* affords meaningful nephroprotection, most likely through its antioxidant constituents.

KEYWORDS: *Cinnamon malabatrum*, gentamicin, nephroprotection, oxidative stress, malondialdehyde, silymarin.

INTRODUCTION
The kidney is central to the elimination of water-soluble waste, the regulation of fluid and electrolyte balance, and the control of arterial pressure. Each organ holds about a million nephrons, working in series to filter plasma, recover useful solutes and excrete the remainder as urine. Renal tissue is also metabolically very active; it secretes erythropoietin, renin and the active form of vitamin D, so that injury to the kidney has consequences well beyond the urinary system.[1] The cells of the proximal tubule are especially vulnerable. Their high metabolic rate, the dense complement of brush-border carriers and the direct contact with filtered solutes mean that any drug excreted by the kidney is likely to be encountered there first, and often at concentrations many times higher than those in plasma.[2]

Drug-induced kidney damage accounts for a sizeable share of acute renal failure seen in hospital practice. The offending agents are varied and include aminoglycosides, non-steroidal anti-inflammatory drugs, calcineurin inhibitors, several antiretrovirals and the platinum-based anticancer drugs.[3,4] In many of these cases the underlying mechanism is similar. Reactive oxygen species are produced faster than the cell can detoxify them, lipids in the membrane peroxidise, mitochondria fail and the cell eventually dies by a mix of necrosis and apoptosis.[5]

Gentamicin is the prototype aminoglycoside and is widely used against serious Gram-negative infection. In the experimental setting it is the agent of choice for studying renal injury because it produces a predictable, dose-related lesion. The cationic drug is filtered by the glomerulus and avidly reabsorbed by megalin–cubilin receptors on the brush border. Once inside the tubular cell, it is sequestered in lysosomes, destabilises membranes, depletes ATP and finally provokes cell death.[6,7] The clinical and laboratory picture is well documented: a rise in serum creatinine and blood urea nitrogen, a fall in creatinine clearance, a polyuric early phase and, on biopsy, cytoplasmic vacuolation, loss of brush border and frank tubular necrosis.[7]

Silymarin, a flavonolignan complex obtained from the seeds of *Silybum marianum*, is the most cited reference nephroprotectant in this paradigm. It scavenges free radicals, stabilises plasma membranes, modulates cytokine signalling and supports cell regeneration,[8] and so makes a sensible positive control for studies of this kind.

Plants rich in polyphenols have attracted growing attention as add-on options for limiting drug-induced renal injury. *Cinnamon malabatrum* (syn. *Cinnamomum malabatrum*; Lauraceae), known in English as wild cinnamon and in Telugu as *Adavilavangapatta*, is an evergreen tree of the Western Ghats. Its leaves contain cinnamaldehyde, eugenol, linalool, caryophyllene, cinnamic acid and a varied collection of flavonoids and tannins.[9,10] Earlier reports describe antihyperlipidaemic, antioxidant, antimicrobial and cytotoxic activities for the leaf extract,[10,11] and a recent review has drawn together its traditional uses and reported pharmacology.[12] In spite of this, a careful study of its protective effect against drug-induced kidney damage has not yet been published. The present work was therefore designed to evaluate, in a Wistar rat model, the nephroprotective activity of the hydroalcoholic leaf extract of *C. malabatrum* against gentamicin, taking silymarin as the reference standard and measuring a panel of biochemical, anti-oxidant and histological end-points.

MATERIALS AND METHODS

Plant material and authentication

Mature, healthy leaves of *Cinnamon malabatrum* were collected from cultivated plants in and around Hyderabad, Telangana, during the post-monsoon months. The plant was identified and authenticated by Dr. K. Madhava Chetty, Assistant Professor, Department of Botany, Sri Venkateshwara University, Tirupati, and a voucher specimen was deposited in the institutional herbarium. Diseased and insect-damaged leaves were rejected. Sound material was shade dried, ground to a coarse powder in a mechanical mill and stored in air-tight glass containers in a cool, dark place until used.

Chemicals and reagents

Gentamicin sulphate (40 mg/ml injection) was purchased from a local pharmacy. Silymarin was procured as a pharmaceutical-grade reagent. Commercial diagnostic kits for the estimation of urea and creatinine were obtained from Erba Diagnostics Mannheim GmbH, Germany. All other chemicals and solvents used in the study were of analytical grade and procured from established suppliers.

Preparation of the hydroalcoholic extract

A 250 g batch of the coarse leaf powder was packed into a Soxhlet thimble and extracted first with petroleum ether (boiling range 60–80°) for about 6 h to remove waxes, fixed oils and other non-polar constituents. The defatted marc was air dried, transferred back to the thimble and extracted with ethanol-water (1:1, v/v) for 18–20 h until the dripping solvent ran colourless. The combined hydroalcoholic filtrate was evaporated to dryness under reduced pressure at 40° on a rotary evaporator. A dark green, semi-solid residue weighing 9.21 g was obtained, giving a yield of 3.68 % w/w on the starting plant material. The dried extract, hereafter referred to as HALCM, was stored at 4° in a desiccator until further use.

Preliminary phytochemical screening

Both the petroleum-ether and the hydroalcoholic fractions were subjected to standard qualitative tests for major secondary metabolites.[13] Alkaloids were detected with Mayer's reagent, glycosides by Baljet's test, carbohydrates by Molisch's test, flavonoids by Shinoda's test, saponins by the froth test, tannins with 5 % ferric chloride solution, phytosterols by the Salkowski reaction and fixed oils by the spot test on filter paper. The findings are summarised in the Results section.

Experimental animals

Adult Wistar albino rats of either sex, weighing 180–200 g, were obtained from an approved animal house. They were housed in clean polypropylene cages at room temperature (22±2°), relative humidity 50–60 % and a 12 h light/dark cycle. Pelleted feed and tap water were given ad libitum. The animals were acclimatised to the laboratory conditions for one week before the start of the study. The protocol was approved by the Institutional Animal Ethics Committee of Malla Reddy College of Pharmacy (IAEC reference number to be inserted at proof stage) and all procedures were carried out in line with the guidelines of the Committee for the Purpose of Control and Supervision of Experiments on Animals (CPCSEA), Government of India.

Experimental design

After the acclimatisation period the rats were randomly distributed into five groups of six animals each. Group I (normal control) received only tap water and standard pellet feed for the 14 d study period. Group II (disease control) received gentamicin sulphate 100 mg/kg, i.p., once daily for the first 7 d. Group III (standard) received

gentamicin (100 mg/kg, i.p., 7 d) along with silymarin 100 mg/kg, p.o., once daily for 14 d. Groups IV and V received gentamicin (100 mg/kg, i.p., 7 d) along with HALCM at 150 mg/kg and 300 mg/kg, p.o., respectively, once daily for 14 d. Body weight was recorded on day 1 and day 14. A 24 h urine sample was collected from each animal on day 14 by housing it singly in a metabolic cage. Urine volume was measured to the nearest 0.1 ml in a graduated cylinder and urinary pH was read at the time of collection on a calibrated dip-stick kit. On day 15 the animals were lightly anaesthetised with ether and blood was withdrawn by cardiac puncture into plain tubes. After clotting at room temperature the serum was separated by centrifuging at 3000 rpm for 15 min at 4° and was used for the estimation of urea and creatinine. Both kidneys were removed, cleared of fat, rinsed in ice-cold saline, blotted on filter paper and weighed. One kidney was fixed in 10 % neutral buffered formalin for histology; the other was homogenised in ice-cold phosphate buffer for the estimation of MDA and reduced glutathione.

Estimation of blood urea nitrogen

BUN was measured by the urease-glutamate dehydrogenase method using a commercial kit and a semi-automated biochemical analyser. The working reagent was made by mixing reagent R1 (Tris buffer, α-ketoglutarate, urease, GLDH) and reagent R2 (NADH) in a 4:1 ratio. For each tube, 1000 µl of the working reagent was incubated with 20 µl of the sample or standard for 20 min, and the absorbance was read at 340 nm. Concentrations were calculated in mg/dl from the standard.

Estimation of serum creatinine

Serum creatinine was estimated by the modified Jaffe method on the same biochemical analyser. The working reagent was made by mixing reagent R1 (sodium hydroxide) and reagent R2 (picric acid) in a 1:1 ratio. To 1000 µl of the working reagent, 20 µl of standard or sample was added; absorbance was read at 505 nm after 10 s. Results were expressed in mg/dl.

Estimation of creatinine clearance

Creatinine clearance was calculated for each animal from the urinary and serum creatinine concentrations and the 24 h urine volume, using the standard expression: creatinine clearance (ml/min) = (urinary creatinine × urine flow)/serum creatinine.

Estimation of malondialdehyde

Renal lipid peroxidation was assessed by quantifying MDA, the principal end product of polyunsaturated fatty acid breakdown. A 10 % w/v kidney homogenate was prepared in ice-cold 0.1 M phosphate buffer, pH 7.4. Proteins were precipitated with 20 % w/v trichloroacetic acid containing 1 mM EDTA. After centrifugation the supernatant was reacted with 0.67 % thiobarbituric acid and heated in a boiling water bath for 15 min. The pink chromogen produced was read at 532 nm against a reagent blank. MDA content was expressed in nmol per ml of homogenate.

Estimation of reduced glutathione

Reduced glutathione was estimated by Ellman's method. To 1.9 ml of phosphate buffer (pH 7.4) was added 0.1 ml of renal supernatant and 0.1 ml of H_2O_2 as substrate; a parallel blank without H_2O_2 was run alongside. The yellow chromogen produced on reaction with 5,5'-dithiobis-(2-nitrobenzoic acid) was read at 412 nm. Results were expressed in µg per mg of tissue.

Histopathological examination

Kidneys fixed in 10 % neutral buffered formalin were processed through graded alcohols, cleared in xylene and embedded in paraffin wax. Sections 4–5 µm thick were cut on a rotary microtome, stained with haematoxylin and eosin and examined under a light microscope at 40× by a histopathologist who was blinded to the treatment groups. Glomerular structure, tubular outline and the presence of vacuolation, congestion, necrosis and inflammatory cells were assessed.

Statistical analysis

Results are reported as mean±SEM for six animals per group. Inter-group comparisons were drawn using one-way analysis of variance followed by Dunnett's multiple comparison test, with the gentamicin (disease control) group as the reference. GraphPad Prism version 10.0 was used for all calculations. A p value less than 0.05 was taken as significant. Significance levels are denoted by *p<0.05, **p<0.01 and ***p<0.001.

RESULTS

Preliminary phytochemical screening

Standard chemical tests gave a clear picture of the two extracts. The petroleum-ether fraction tested positive only for alkaloids and flavonoids. The hydroalcoholic fraction was a much richer source of secondary metabolites and gave positive reactions for carbohydrates, glycosides, alkaloids, flavonoids, phenolics, tannins, saponins, proteins with free amino acids and terpenoids. Steroids, fixed oils and resins were not detected in either fraction. The full set of results is presented in Table 1.

Effect on body weight

All groups had comparable body weights at the start of the study. By day 14 the normal control animals had gained 67.77 % over their initial weight, as expected for healthy growing rats of this age. In contrast, the gentamicin group had lost roughly 7 % of starting body weight, in line with the systemic toxicity that follows aminoglycoside dosing. Both the silymarin group and the two test groups showed a steady gain in body weight, with the gain in the HALCM 300 mg/kg group (5.20 %) being closer to that of silymarin (8.82 %) than to that of the lower extract dose (3.69 %). The results are given in Table 2.

Effect on blood urea nitrogen and serum creatinine

Serum BUN rose sharply in the gentamicin animals (34.67±0.47 mg/dl), almost double the value seen in the normal controls (18.56±0.67 mg/dl). Silymarin pulled BUN back to a value (16.45±0.39 mg/dl) that was close to that of the normal group. Both doses of HALCM produced a similar correction; the 300 mg/kg dose (18.63±0.29 mg/dl) was marginally better than the 150 mg/kg dose (19.77±0.48 mg/dl). Serum creatinine followed the same pattern. The gentamicin group showed a more-than-three-fold rise (2.10±0.05 mg/dl) over the normal control (0.65±0.05 mg/dl), and the rise was significantly attenuated by silymarin and by both doses of the extract, with values of 1.10±0.04 mg/dl in the HALCM 300 mg/kg group closely matching the silymarin value of 1.00±0.06 mg/dl. The data are summarised in Table 3 and Table 4.

Effect on creatinine clearance

Creatinine clearance, taken here as a surrogate of glomerular filtration rate, fell from 1.75±0.51 ml/min in the normal controls to 0.50±0.44 ml/min in the gentamicin group. Silymarin doubled this depressed value (1.05±0.56 ml/min). The HALCM 300 mg/kg group reached almost the same level (0.95±0.98 ml/min), while the 150 mg/kg dose produced a smaller but still significant rise (0.75±0.10 ml/min). The figures are given in Table 5.

Effect on renal malondialdehyde and reduced glutathione

Renal MDA, an index of lipid peroxidation, rose from 104.10±2.44 nM in the normal controls to 186.30±2.14 nM in the gentamicin group, a clear indication of intense oxidative stress within the renal tissue. Silymarin brought MDA back to 105.70±1.98 nM. HALCM produced a dose-related fall, with the 300 mg/kg dose (110.50±9.18 nM) almost matching the silymarin value and the 150 mg/kg dose producing a partial recovery (119.90±22.45 nM). The renal pool of reduced glutathione moved in the opposite direction, as anticipated. Gentamicin depleted GSH from 24.50±1.02 µg/mg tissue to 14.36±2.00 µg/mg; silymarin and both doses of HALCM restored it to near-control levels. Details are given in Tables 6 and 7.

Effect on urine output and urinary pH

The polyuric response that accompanies aminoglycoside toxicity was evident in the disease group, with the 24 h urine volume rising from 3.27±0.15 ml in the controls to 5.78±0.60 ml after gentamicin. Treatment with silymarin and with both doses of HALCM brought the urine volume back to near-normal values. The urinary pH fell from 7.40±0.43 to 4.83±0.32 in the gentamicin group, reflecting impaired tubular acid handling, and was restored by all three treatments. Data are given in Tables 8 and 9.

Histopathological observations

Light-microscopic examination of haematoxylin- and eosin-stained renal sections provided strong morphological support for the biochemical findings (fig. 1). In the normal control kidney, the cortex showed well-circumscribed glomeruli with intact Bowman's capsules, proximal and distal tubules lined by an organised cuboidal epithelium with clear, patent lumina and an unremarkable interstitium. There was no vacuolation or necrosis. Sections from the gentamicin group showed the classical picture of acute tubular injury. Many of the proximal tubules had lost their brush border, the cytoplasm showed prominent vacuolation and there was glomerular congestion in some fields. Sections from animals that received silymarin together with gentamicin were close to normal in appearance; the tubular epithelium was largely intact and glomerular outlines were well preserved. Animals on the 150 mg/kg dose of HALCM showed an intermediate picture, with a noticeable reduction in tubular necrosis and a partial return of glomerular structure but with some residual vacuolation in scattered fields. At the higher dose (300 mg/kg) the renal architecture closely resembled that of the normal control, with only minimal necrosis. The dose-related pattern seen on histology paralleled that of the biochemical end-points.

Table 1: Preliminary phytochemical screening of the petroleum-ether and hydroalcoholic leaf extracts of Cinnamon malabatrum.

Chemical constituent	Petroleum-ether extract	Hydroalcoholic extract
Carbohydrates	-	+
Glycosides	-	+
Alkaloids	+	+
Flavonoids	+	+
Phenolics	-	+
Tannins	-	+
Steroids	-	-
Saponins	-	+
Proteins and free amino acids	-	+
Terpenoids	-	+
Fixed oils and resins	-	-

+, Present; -, absent.

Table 2: Effect of silymarin and HALCM on body weight in gentamicin-induced nephrotoxic rats.

Group	Treatment	Initial weight (g)	Final weight (g)	Change	% Change
I	Normal control	180.5±4.24	302.5±3.24	Increased	67.77***
II	GEN (100 mg/kg, i.p.)	190.3±3.86	176.6±3.26	Decreased	-7.19
III	Silymarin (100 mg/kg, p.o.) + GEN	188.1±4.19	204.7±3.81	Increased	8.82***
IV	HALCM (150 mg/kg, p.o.) + GEN	189.3±3.87	196.3±4.98	Increased	3.69*
V	HALCM (300 mg/kg, p.o.) + GEN	192.8±4.19	202.6±3.13	Increased	5.20**

Values are mean±SEM (n=6); ***p<0.001, **p<0.01, *p<0.05 versus the gentamicin (GEN) group (one-way ANOVA followed by Dunnett's multiple comparison test). HALCM, hydroalcoholic leaf extract of *Cinnamon malabatrum*.

Table 3: Effect of silymarin and HALCM on blood urea nitrogen in gentamicin-induced nephrotoxic rats.

Group	Treatment	BUN (mg/dl)
I	Normal control	18.56±0.67***
II	GEN (100 mg/kg, i.p.)	34.67±0.47
III	Silymarin (100 mg/kg, p.o.) + GEN	16.45±0.39***
IV	HALCM (150 mg/kg, p.o.) + GEN	19.77±0.48**
V	HALCM (300 mg/kg, p.o.) + GEN	18.63±0.29**

Values are mean±SEM (n=6); ***p<0.001, **p<0.01 versus the GEN group.

Table 4: Effect of silymarin and HALCM on serum creatinine in gentamicin-induced nephrotoxic rats.

Group	Treatment	Serum creatinine (mg/dl)
I	Normal control	0.65±0.05***
II	GEN (100 mg/kg, i.p.)	2.10±0.05
III	Silymarin (100 mg/kg, p.o.) + GEN	1.00±0.06***
IV	HALCM (150 mg/kg, p.o.) + GEN	1.45±0.07**
V	HALCM (300 mg/kg, p.o.) + GEN	1.10±0.04***

Values are mean±SEM (n=6); ***p<0.001, **p<0.01 versus the GEN group.

Table 5: Effect of silymarin and HALCM on creatinine clearance in gentamicin-induced nephrotoxic rats.

Group	Treatment	Creatinine clearance (ml/min)
I	Normal control	1.75±0.51***
II	GEN (100 mg/kg, i.p.)	0.50±0.44
III	Silymarin (100 mg/kg, p.o.) + GEN	1.05±0.56**
IV	HALCM (150 mg/kg, p.o.) + GEN	0.75±0.10*
V	HALCM (300 mg/kg, p.o.) + GEN	0.95±0.98**

Values are mean±SEM (n=6); ***p<0.001, **p<0.01, *p<0.05 versus the GEN group.

Table 6: Effect of silymarin and HALCM on renal malondialdehyde in gentamicin-induced nephrotoxic rats.

Group	Treatment	MDA (nM)
I	Normal control	104.10±2.44***
II	GEN (100 mg/kg, i.p.)	186.30±2.14
III	Silymarin (100 mg/kg, p.o.) + GEN	105.70±1.98***
IV	HALCM (150 mg/kg, p.o.) + GEN	119.90±22.45**
V	HALCM (300 mg/kg, p.o.) + GEN	110.50±9.18**

Values are mean±SEM (n=6); ***p<0.001, **p<0.01 versus the GEN group.

Table 7: Effect of silymarin and HALCM on renal reduced glutathione in gentamicin-induced nephrotoxic rats.

Group	Treatment	GSH (µg/mg tissue)
I	Normal control	24.50±1.02***
II	GEN (100 mg/kg, i.p.)	14.36±2.00
III	Silymarin (100 mg/kg, p.o.) + GEN	25.60±1.02***
IV	HALCM (150 mg/kg, p.o.) + GEN	23.36±1.20**
V	HALCM (300 mg/kg, p.o.) + GEN	24.30±1.20***

Values are mean±SEM (n=6); ***p<0.001, **p<0.01 versus the GEN group.

Table 8: Effect of silymarin and HALCM on 24 h urine output in gentamicin-induced nephrotoxic rats.

Group	Treatment	Urine output (ml/24 h)
I	Normal control	3.27±0.15***
II	GEN (100 mg/kg, i.p.)	5.78±0.60
III	Silymarin (100 mg/kg, p.o.) + GEN	3.70±0.63***
IV	HALCM (150 mg/kg, p.o.) + GEN	3.56±0.46***
V	HALCM (300 mg/kg, p.o.) + GEN	3.33±0.53***

Values are mean±SEM (n=6); ***p<0.001 versus the GEN group.

Table 9: Effect of silymarin and HALCM on urinary pH in gentamicin-induced nephrotoxic rats.

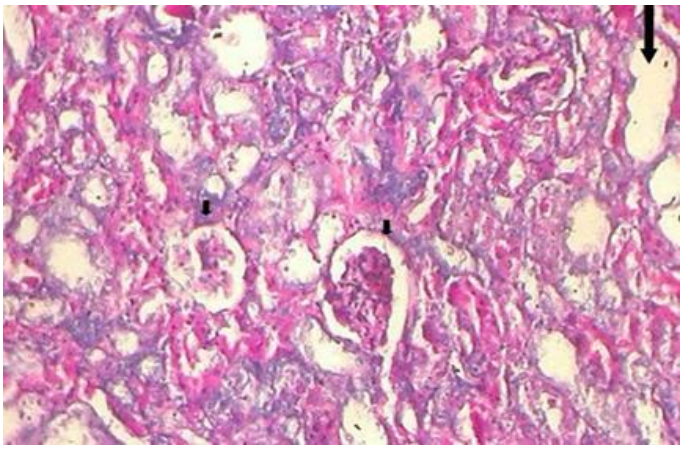
Group	Treatment	Urinary pH
I	Normal control	7.40±0.43***
II	GEN (100 mg/kg, i.p.)	4.83±0.32
III	Silymarin (100 mg/kg, p.o.) + GEN	7.65±0.32***
IV	HALCM (150 mg/kg, p.o.) + GEN	6.95±0.56**
V	HALCM (300 mg/kg, p.o.) + GEN	7.00±0.38***

Values are mean±SEM (n=6); ***p<0.001, **p<0.01 versus the GEN group.

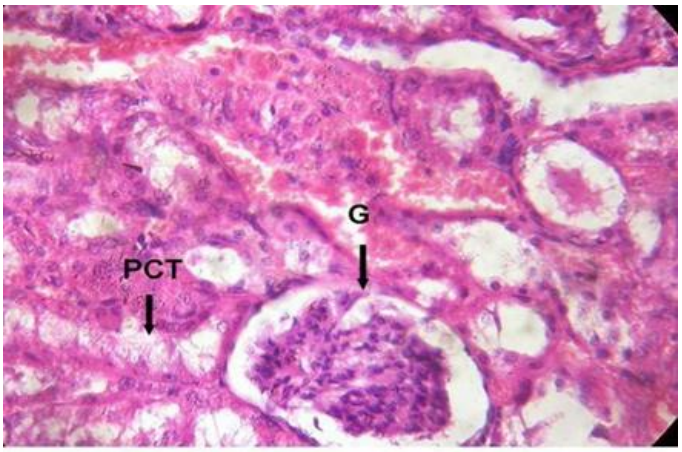
Legend to figure

Fig. 1: Photomicrographs of haematoxylin- and eosin-stained kidney sections (40× magnification). **(A)** Normal control showing intact glomeruli (G) and well-organised tubular architecture with clear lumina; **(B)** gentamicin group (100 mg/kg, i.p.) showing cytoplasmic vacuolation of the proximal convoluted tubule (PCT), loss of brush border and glomerular (G) congestion; **(C)** silymarin (100 mg/kg, p.o.) plus gentamicin showing near-normal tubular and glomerular outlines with a marked reduction in vacuolation; **(D)** HALCM (150 mg/kg, p.o.) plus gentamicin showing moderate restoration of tubular morphology with partially preserved glomeruli (G) and PCT; **(E)** HALCM (300 mg/kg, p.o.) plus gentamicin showing pronounced restoration of renal architecture and minimal residual necrosis.

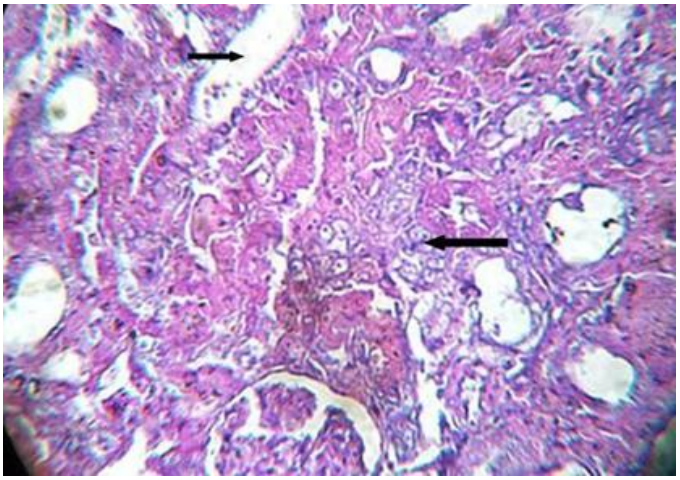
Fig. 1



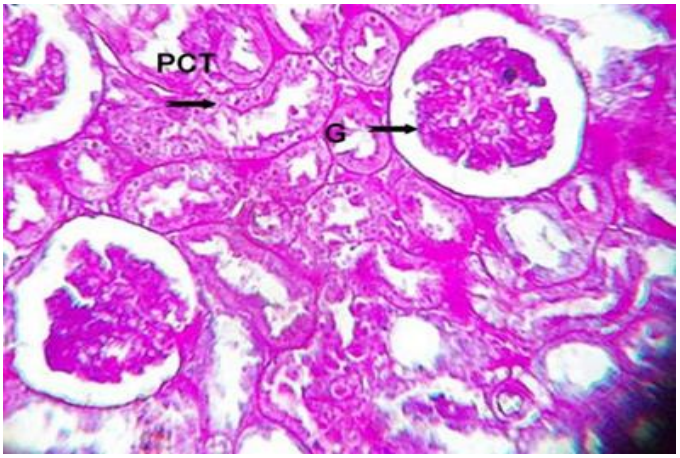
(A) Normal control



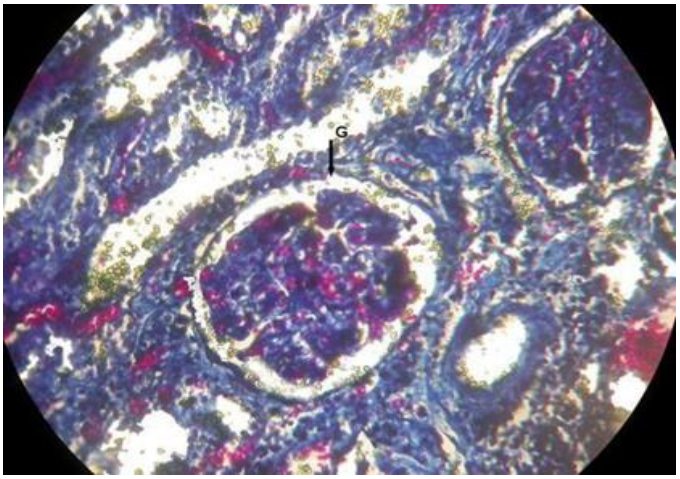
(B) Gentamicin 100 mg/kg, i.p.



(C) Silymarin 100 mg/kg, p.o. + GEN



(D) HALCM 150 mg/kg, p.o. + GEN



(E) HALCM 300 mg/kg, p.o. + GEN

DISCUSSION

Aminoglycoside-induced renal injury is a recurring clinical problem, complicating around 10–25 % of treatment courses with these antibiotics in spite of careful dosing and therapeutic monitoring.[7] Gentamicin in particular accumulates in the proximal tubular cell, where it sets off a mitochondrial source of reactive oxygen species; the resulting oxidative stress, coupled with falling ATP, drives lipid peroxidation, lysosomal rupture and cell death.[5,6] In the present work, intraperitoneal gentamicin at 100 mg/kg for 7 d reproduced this picture very faithfully. The disease control animals showed the expected rise in BUN, serum creatinine and renal MDA, a marked fall in body weight, creatinine clearance, GSH, urine output (after the initial polyuric phase) and urinary pH, and, on light microscopy, the cytoplasmic vacuolation and glomerular congestion that are characteristic of the model.

Treatment with the hydroalcoholic leaf extract of *C. malabatrum* attenuated all of these changes in a dose-related fashion. At 150 mg/kg the effects were modest but still significant for most parameters. At 300 mg/kg the protection was clearly stronger, and for several end-points the values were not very different from those obtained with silymarin. The fall in BUN and creatinine, with the parallel recovery of creatinine clearance, suggests that the extract preserves glomerular filtration. The histology supports this interpretation: in the 300 mg/kg group the cortex looked close to normal, and the tubular outlines, brush border and glomerular structure were largely intact.

Oxidative damage is the central event in gentamicin nephrotoxicity,[5,14] and the data on MDA and GSH provide the most direct evidence that the extract is acting through this pathway. Renal MDA, raised almost two-fold by gentamicin, was returned to near-normal values by the 300 mg/kg dose, and the parallel restoration of GSH content shows that the antioxidant reserve was effectively rebuilt. The phytochemical analysis indicates the most likely chemical basis. The hydroalcoholic extract is rich in flavonoids, phenolics and tannins, all of which are well known free-radical scavengers and inducers of the cellular antioxidant defence system.[10,11,15] Cinnamaldehyde and eugenol, both reported as constituents of *Cinnamon malabatrum*, have been shown in independent studies to activate the Nrf2/Keap1 axis and to suppress NF-κB-driven inflammation in models of renal injury,[10] and either or both of these mechanisms may be in play here.

Functional restoration of the tubular compartment was also evident in the urinary data. The early polyuric phase of gentamicin toxicity arises because the damaged proximal tubule fails to reabsorb water and electrolytes; the marked acidification of the urine reflects a parallel failure of the distal nephron to acidify and concentrate. Both of these abnormalities were reversed by HALCM, with values at the higher dose close to those of the normal animals.

The present findings sit comfortably with a wider body of work on plant-derived nephroprotection. Diosgenin, the aqueous extract of *Pimpinella anisum*, and silymarin itself have all been shown to limit gentamicin-induced renal injury through broadly similar antioxidant mechanisms.[8,16,17] Working in the very same model, a recent study found that a hydroalcoholic extract of *Amaranthus roxburghianus* Nevski restored renal function and the tissue antioxidant pool in gentamicin-treated Wistar rats,[18] an effect in keeping with the long traditional use of this species.[19] Herbal preparations made by the same alcoholic and aqueous route have likewise shown organ-protective and antiurolithic activity, as reported for *Allium cepa*.[20,21] The novelty of the present study lies in the formal demonstration that *C. malabatrum* leaf extract, traditionally used for diverse complaints but not previously screened against drug-induced kidney damage, behaves in a comparable manner. The dose-response observed here is encouraging and lays the ground for follow-up work, both on the mechanism (including the role of individual phytoconstituents such as cinnamaldehyde, eugenol and quercetin glycosides) and on the question of optimal dose, duration and route of administration.

A few limitations of the present study should be noted. The work was carried out in a single rodent species and over a relatively short timeframe; long-term toxicity and the influence of comorbidities such as diabetes and hypertension on the protective effect were not assessed. The use of a 50:50 ethanol-water mixture, while convenient for capturing both polar and moderately polar constituents, leaves open the question of which exact compounds are responsible for the activity. Bioassay-guided fractionation, coupled with quantification of the major flavonoids and phenolics, would be a sensible next step.

CONCLUSION

The present results indicate that the hydroalcoholic leaf extract of *Cinnamon malabatrum* provides meaningful protection against gentamicin-induced kidney damage in rats. The activity is dose-related, parallels the protective profile of silymarin and is well supported by both biochemical and histological end-points. Subject to further mechanistic study and dose optimisation, *C. malabatrum* leaf merits attention as a potential herbal adjunct for limiting drug-induced renal injury.

ACKNOWLEDGEMENT

The authors thank the management and the Principal of Malla Reddy College of Pharmacy, Maisammaguda, Secunderabad, for the laboratory facilities and the infrastructure provided for this study. Sincere thanks are also due to Dr. K. Madhava Chetty, Sri Venkateshwara University, Tirupati, for authenticating the plant material, and to the staff of the Department of Pharmacology for their help with the animal work.

FUNDING

This work did not receive any specific grant from funding agencies in the public, commercial or not-for-profit sectors.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

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