Original Article

Nephroprotective and Cytotoxic Assessment of *Moringa concanensis* Leaf Extract in Gentamicin-Induced Renal Injury in Rats

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ABSTRACT

Background: Gentamicin-induced nephrotoxicity is a significant clinical concern, characterized by tubular necrosis and impaired renal function. This study aimed to evaluate the *in vitro* antioxidant and cytotoxic properties, along with the *in vivo* nephroprotective potential of Ethanolic Leaf Extract of *Moringa concanensis* (ELMC), against gentamicin-induced renal injury in rats. **Materials and Methods:** ELMC was subjected to preliminary phytochemical screening to identify its active constituents. Antioxidant activity was assessed using the DPPH free radical scavenging assay, and cytotoxicity was evaluated via the MTT assay on HEK 293 cells. For *in vivo* analysis, 30 male Wistar rats were randomly divided into five groups (n=6): Group 1 (normal control), Group 2 (gentamicin 100 mg/kg i.p. for 10 days), Groups 3 and 4 (ELMC at 200 mg/kg and 400 mg/kg p.o. for 16 days, respectively, alongside gentamicin), and Group 5 (ascorbic acid 45 mg/kg p.o. as standard). Renal function was assessed by measuring serum creatinine, uric acid, and Blood Urea Nitrogen (BUN), while kidney homogenates were analyzed for Malondialdehyde (MDA), Catalase (CAT), and Superoxide Dismutase (SOD). Histopathological examination of kidney tissues was performed using Hematoxylin and Eosin (H&E) staining. **Results:** Phytochemical analysis revealed the presence of alkaloids, carbohydrates, flavonoids, and tannins in ELMC. The extract demonstrated notable antioxidant activity and exhibited no cytotoxic effects on HEK 293 cells. *In vivo*, ELMC treatment significantly improved renal biomarkers and enhanced antioxidant enzyme levels, while preserving renal histoarchitecture in comparison to the gentamicin-only group. **Conclusion:** ELMC exhibits potent nephroprotective effects against gentamicin-induced renal damage, likely attributed to its antioxidant and anti-inflammatory properties. These findings support its potential as a natural therapeutic agent; however, further mechanistic and clinical studies are necessary to validate its efficacy.

Keywords: Gentamicin, *Moringa concanensis*, Nephrotoxicity, Renal function.

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INTRODUCTION

Nephrotoxicity refers to the deleterious effects of various substances on kidney function, which can manifest as acute or chronic kidney injury, impaired glomerular filtration, or other forms of renal dysfunction.[1] Among the agents known to cause nephrotoxicity, Gentamicin (GM), a widely used aminoglycoside antibiotic, is notable for its broad-spectrum antibacterial activity, rapid bactericidal effect, low resistance rate, and affordability. However, its clinical use is limited by its nephrotoxic potential, with renal damage occurring in approximately 10-20% of patients receiving GM therapy.[2] In addition to gentamicin, several other commonly used drugs are associated with nephrotoxic side effects, particularly with chronic use. These include Nonsteroidal Anti-Inflammatory Drugs (NSAIDs) such as ibuprofen, naproxen, and aspirin; antibiotics like vancomycin and sulfonamides; chemotherapeutic agents including cisplatin and methotrexate; antiviral drugs like acyclovir; and antifungal agents such as amphotericin B.[2] Currently, the management of drug-induced nephrotoxicity relies on interventions such as intravenous fluid therapy, diuretics (e.g., furosemide), N-acetylcysteine, and antioxidant supplementation (e.g., Vitamins C and E). While these treatments offer some therapeutic benefit, they may also pose additional risks and adverse effects.

Given these limitations, there is an urgent need for alternative therapeutic strategies, particularly from natural sources. Traditional systems of medicine-such as Ayurveda, Siddha, Unani, and Homeopathy-emphasize the rational use of medicinal plants, animals, and minerals. The increasing reliance on herbal

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medicine can be attributed to its protective effects against organ toxicity, including nephrotoxicity, and its relatively low side-effect profile.[3] Several medicinal plants have been investigated for their nephroprotective potential, including *Matricaria chamomilla, Euterpe oleracea, Sophora alopecuroides*, and *Betula alba*.[4]

Moringa concanensis, a lesser-known member of the *Moringa* genus (commonly known as Konkan Moringa), belongs to the family *Moringaceae*. The *Moringa* genus is globally recognized for its nutritional richness, water purification capabilities, and medicinal applications. Various parts of the plant, including the leaves, seeds, and pods, are consumed for their high nutrient content. Traditionally, *M. concanensis* has been utilized to treat ailments such as colds, coughs, toothaches, skin rashes, and body pain, and also as a natural disinfectant. The plant is known to contain a wide array of bioactive phytochemicals such as flavonoids, tannins, alkaloids, saponins, and phenolic compounds, which contribute to its reported antioxidant, anti-inflammatory, and antimicrobial properties.[3] In addition to these, *Moringa concanensis* has demonstrated other pharmacological activities including antioxidant,[5] anti-inflammatory,[6] antiparkinsonian,[7] immunomodulatory,[8] anticonvulsant,[9] anti-arthritic,[10] anti-fertility,[11] anti-hyperglycemic,[12] and anti-anemic effects.[13] However, to date, no comprehensive study has investigated the protective effects of *Moringa concanensis* against gentamicin-induced nephrotoxicity.

Therefore, the present study was designed to evaluate the nephroprotective efficacy of ethanolic leaf extract of *Moringa concanensis* in a rat model of GM-induced nephrotoxicity. The investigation included *in vitro* antioxidant assays, cytotoxicity analysis on HEK 293 cells, measurement of renal biomarkers, assessment of oxidative stress parameters, and histopathological examination of kidney tissue. This study aims to explore the therapeutic potential of *M. concanensis* as a plant-based intervention for mitigating drug-induced renal injury.

MATERIALS AND METHODS

Plant collection and authentication

Fresh *Moringa concanensis* leaves were collected from ICAR-IIHR, (Indian Institute of Horticultural Research) Bengaluru, and authenticated by a Senior Scale Scientist in Flowers and Medicinal Crops at ICAR-IIHR, Bengaluru.

Extract Preparation

The extraction process began with drying and powdering 500 g of *Moringa concanensis* leaves. The powdered material was then subjected to continuous hot extraction using 90% ethanol in a Soxhlet apparatus for 48 hr. The obtained extract was concentrated using a rotary evaporator (Rotavapor) under reduced pressure to remove excess solvent. The resulting semi-solid mass was subsequently freeze-dried at -80ºC through lyophilization to obtain a dry powdered extract. The final yield of the ethanolic leaf extract of *Moringa concanensis* was 25 g (Figure 1).

In vitro Antioxidant Activity

DPPH Free Radical Scavenging Assay

The antioxidant potential of the extract was evaluated using the 2,2-Diphenyl-1-Picrylhydrazyl (DPPH) free radical scavenging assay, which assesses the ability of antioxidants to reduce DPPH, resulting in a color change from purple to yellow. A 0.1 mM DPPH solution was prepared in 95% ethanol and mixed with various concentrations (0.1, 0.15, and 0.2 mg/mL) of the plant extract and ascorbic acid (used as a standard). The mixtures were incubated in the dark at room temperature for 30 min. Absorbance was then measured at 517 nm using a UV-vis spectrophotometer.[14] The percentage of DPPH radical scavenging activity was calculated using the following formula:

$$\%DPPH\ inhibition = \frac{A - B}{A} \times 100$$

Cell Viability Assay

The cytotoxicity of the extract was assessed using the MTT assay on HEK 293 cells. Cells were cultured in Minimum Essential Medium (MEM) supplemented with 10% Fetal Bovine Serum (FBS) and non-essential amino acids under standard conditions (37ºC, 5% CO_2). Approximately 5×10^4 cells per well were seeded into a 96-well plate and allowed to adhere overnight. The cells were then treated with varying concentrations of the test extract (ranging from 0.976 to 500 µg/mL) and incubated for 24 hr.

Following treatment, 20 µL of MTT solution (5 mg/mL) was added to each well and incubated for an additional 4 hr to allow the formation of formazan crystals. The medium was then removed, and the crystals were solubilized using DMSO.[15] Absorbance was measured at 570 nm using a microplate reader. Cell viability was calculated using the formula:

$$\%\ \text{viability} = \frac{Abs.of\ sample}{Abs.of\ control} \times 100$$

Animals

Healthy adult male albino Wistar rats, weighing between 200-250 g, were obtained from a certified breeder (Vaarunya Biolabs Pvt. Ltd., Bengaluru). The animals were housed in standard polypropylene cages under controlled laboratory conditions, with a 12-hr light/dark cycle, ambient temperature maintained at 23±2ºC, and relative humidity of 55±5%. Rats were provided with a standard pellet diet and had *ad libitum* access to clean drinking water. All experimental procedures were conducted in accordance with institutional ethical guidelines and approved by the relevant animal ethics committee.

Experimental Design

The rats were randomly divided into five groups (n=6 per group), as illustrated in Figure 2:

Group 1 (Normal Control): Received no treatment and served as the baseline group.

Group 2 (Gentamicin Control): Received Gentamicin (GM) at a dose of 100 mg/kg body weight intraperitoneally (i.p.) from day 6 to day 15 to induce nephrotoxicity.[16]

Group 3 (ELMC Low Dose+GM): Treated orally with Ethanolic Leaf Extract of *Moringa concanensis* (ELMC) at 200 mg/kg body weight daily for 16 days. Gentamicin (100 mg/kg i.p.) was administered from day 6 to day 15.[9]

Group 4 (ELMC High Dose+GM): Treated orally with ELMC at 400 mg/kg body weight daily for 16 days, along with gentamicin (100 mg/kg i.p.) from day 6 to day 15.[9]

Group 5 (Standard Treatment+GM): Received ascorbic acid orally at a dose of 45 mg/kg body weight daily for 16 days, with gentamicin (100 mg/kg i.p.) administered from day 6 to day 15.[17]

Serum Collection and Analysis

Blood samples were collected from the retro-orbital plexus of anesthetized rats using a capillary tube. The samples were centrifuged at 12,000 rpm for 15 min at 4ºC to separate the serum. The obtained serum was aliquoted and stored at -20ºC until further biochemical analysis.[18]

Tissue Preparation for Homogenate and Histopathological Studies

Post-euthanasia, the left kidney was excised, rinsed with ice-cold Phosphate-Buffered Saline (PBS), and homogenized using a tissue homogenizer. The homogenate was centrifuged at 10,000 rpm for 10 min at 4ºC, and the supernatant was collected and stored at -80ºC for the estimation of antioxidant and oxidative stress markers. The right kidney was fixed in 10% formaldehyde for histopathological evaluation.[16]

Estimation of Biochemical Parameters

Serum levels of creatinine, Blood Urea Nitrogen (BUN), and uric acid were estimated using commercially available diagnostic kits, following the manufacturer's protocols. All assays were performed colorimetrically using a spectrophotometer.

Estimation of Antioxidant Enzyme Activity

Superoxide Dismutase (SOD): Activity was assessed by the Nitroblue Tetrazolium (NBT) reduction method as described by Beauchamp and Fridovich.[19]

Catalase (CAT): Activity was determined based on the decomposition of hydrogen peroxide, using the method described by Chance and Maehly.[20]

Estimation of Oxidative Stress Marker

Lipid peroxidation was evaluated by quantifying Malondialdehyde (MDA) levels through the Thiobarbituric Acid Reactive Substances (TBARS) assay.[21]

Histopathological Examination

For histological analysis, right kidney tissues fixed in 10% formaldehyde were processed and embedded in paraffin wax. Sections of 5 µm thickness were cut using a microtome, mounted on glass slides, and stained with Hematoxylin and Eosin (H&E). The stained sections were observed under a light microscope to assess morphological alterations.[22]

Statistical Analysis

All experimental data are expressed as Mean±Standard Error of the Mean (SEM), with n=6 per group. Statistical comparisons among groups were performed using One-Way Analysis of Variance (ANOVA) followed by Tukey's *post hoc* test for multiple comparisons. A p-value <0.05 was considered statistically significant. Analyses were conducted using GraphPad Prism software, version 8.0.2.

RESULTS

Phytochemical Screening

Preliminary phytochemical analysis of the Ethanolic Leaf Extract of *Moringa concanensis* (ELMC) revealed the presence of key bioactive constituents, including alkaloids, carbohydrates, flavonoids, and tannins (Table 1).

Effect of ELMC on DPPH Free Radical Scavenging Activity

The ethanolic leaf extract of *Moringa concanensis* exhibited notable *in vitro* antioxidant activity, as demonstrated by its DPPH free radical scavenging potential. The extract showed a dose-dependent increase in scavenging activity, which was comparable to the standard antioxidant, ascorbic acid (Table 2).

Effect of ELMC on Cell Viability

Treatment of HEK 293 cells with various concentrations of ELMC (up to 500 µg/mL) did not result in significant cytotoxicity. Even at the highest tested concentration, the extract maintained high levels of cell viability, indicating its safety and biocompatibility (Figures 3 and 4). These findings suggest that ELMC is non-toxic to normal human kidney cells within the tested concentration range.

Effect of ELMC on Serum Biochemical Parameters

The impact of ELMC on serum biochemical markers is illustrated in Figure 5. Gentamicin (GM)-treated rats exhibited a significant elevation in Blood Urea Nitrogen (BUN), creatinine, and uric acid levels (###p<0.001) when compared to the Normal Control

(NC) group, indicating renal impairment. However, treatment with ELMC at both 200 mg/kg and 400 mg/kg doses, as well as the standard treatment with ascorbic acid, significantly attenuated these elevations (**$p<0.05$), suggesting a nephroprotective effect of the extract.

Effect of ELMC on Antioxidant Enzyme Activity and Lipid Peroxidation

The effect of ELMC on antioxidant enzyme levels and lipid peroxidation is presented in Figure 6. The Gentamicin (GM) group exhibited a significant increase in Malondialdehyde (MDA) levels (###$p<0.001$), along with a marked decrease in Catalase (CAT) and Superoxide Dismutase (SOD) levels (###$p<0.001$) compared to the Normal Control (NC) group, indicating elevated oxidative stress. Treatment with ELMC at 200 mg/kg and 400 mg/kg doses, as well as the standard ascorbic acid group, resulted in a significant reduction in MDA levels and a corresponding increase in CAT and SOD activities (**$p<0.05$), suggesting the antioxidant and protective effects of ELMC against gentamicin-induced oxidative damage.

Histopathological Studies

Histopathological observations of renal tissues are presented in Figure 7. The Gentamicin (GM) group exhibited marked renal damage characterized by severe tubular degeneration, vascular congestion, and moderate interstitial inflammation. In contrast, kidney sections from the ELMC low-dose group (200 mg/kg) showed relatively preserved architecture with glomerular hypercellularity and only mild interstitial inflammation. Notably, the high-dose ELMC group (400 mg/kg) demonstrated

Figure 1: Extraction process of *Moringa concanensis* Ethanolic Leaves.

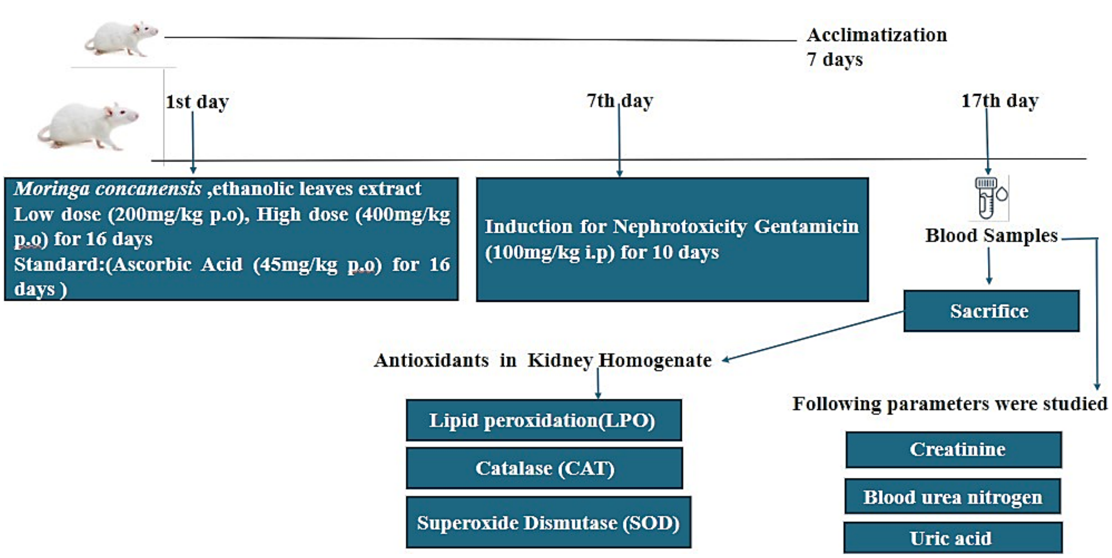

Figure 2: Experimental design.

near-normal histological features, with well-preserved tubular structures and glomeruli, and no significant pathological abnormalities. These findings support the nephroprotective effect of *Moringa concanensis* in mitigating gentamicin-induced renal injury.

DISCUSSION

India is home to approximately 8,000 species of medicinal plants, many of which possess potent natural antioxidant properties that enhance therapeutic efficacy with fewer side effects compared to synthetic drugs.[23] *Moringa concanensis*, commonly known as Konkan Moringa, is native to the Western Ghats and has long been used in traditional medicine for its nutritional and therapeutic properties. Previous studies have documented its antioxidant and anti-inflammatory effects.[5,6]

Antioxidants play a critical role in neutralizing free radicals, which are implicated in the pathogenesis of various diseases such as cardiovascular disorders, aging, cancer, genetic mutations, neurodegenerative diseases, and inflammation.[24] The antioxidant potential of compounds is frequently assessed using the DPPH radical scavenging assay. Similarly, cytotoxicity is evaluated using the MTT assay, which measures cellular metabolic activity as an indicator of cell viability.[25] In the present study, ELMC exhibited notable *in vitro* antioxidant activity, particularly at a concentration of 0.2 mg/mL, demonstrating DPPH radical scavenging capacity comparable to that of ascorbic acid. Moreover, ELMC did not exhibit cytotoxic effects on HEK 293 cells across a wide range of concentrations, confirming its safety and biocompatibility.

Gentamicin (GM) is a widely used aminoglycoside antibiotic known to induce nephrotoxicity depending on the dosage and duration of treatment.[26] Typically, renal impairment is observed after 5-7 days of GM administration at doses ranging from 80 to 150 mg/kg.[27] In our study, administration of GM at 100 mg/kg i.p. for 10 days successfully induced nephrotoxicity, as evidenced by elevated levels of serum biomarkers and histological changes.[16]

The nephroprotective potential of ELMC was evaluated using this GM-induced model. As expected, the GM-treated group showed significantly elevated levels of Blood Urea Nitrogen (BUN), serum creatinine, and uric acid compared to the normal control group, indicating impaired renal function.[28] These findings align with existing literature reporting increased serum biomarkers in GM-induced nephrotoxicity.[29,30] Treatment with ELMC at both low (200 mg/kg) and high (400 mg/kg) doses, as well as the standard antioxidant ascorbic acid, significantly reduced these elevated serum levels (**p<0.05), suggesting restoration of renal

Table 1: Preliminary analysis of ELMC.

Test	Raegent	Indication
Alkaloids	Dragendorff 's test	++
	Mayer's test	++
	Hager's test	++
Carbohydrates	Molish test	++
	Benedict's test	++
	Fehling's test	++
Flavonoids	Alkaline reagent test	++
	Ferric chloride test	++
Tannins	Ferric chloride test	++
	Lead acetate test	++
Steroids	Salkowski test	++

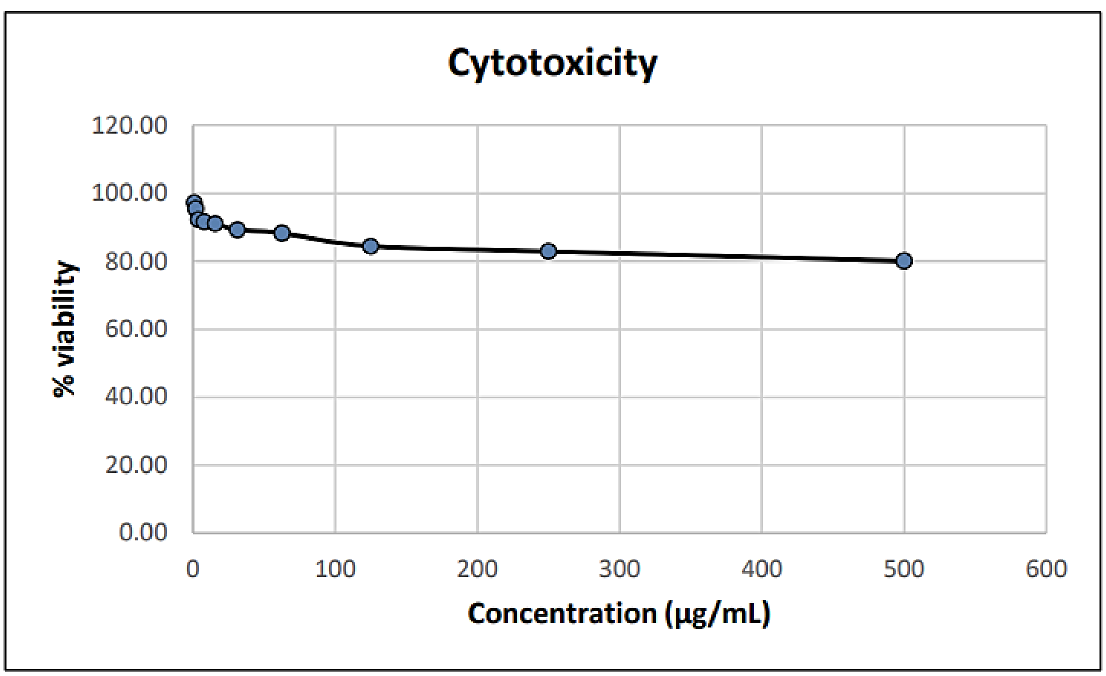

Figure 3: Cytotoxicity of ELMC.

Table 2: Effect of ELMC on DPPH assay.

Sl. No.	Test substance	Conc. (mg/mL)	DPPH inhibition (%)
1	ELMC	0.1	24.54
		0.15	45.48
		0.2	68.25
2	Ascorbic acid (standard)	0.1	50.55
		0.15	68.12
		0.2	88.62

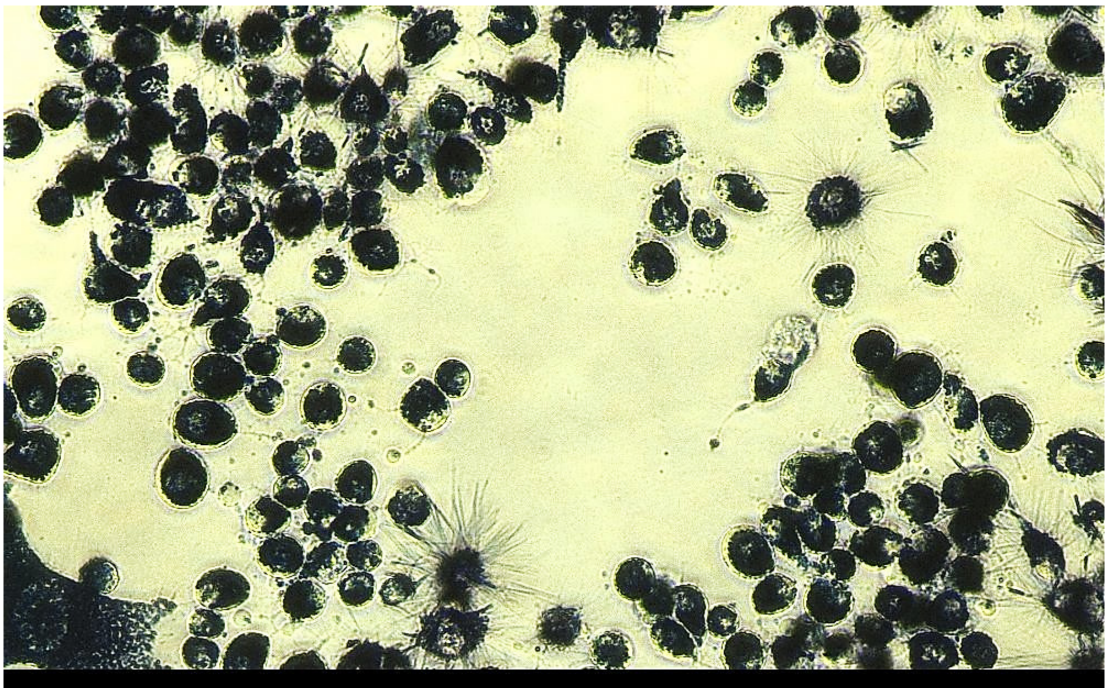

Figure 4: Test substance-treated (500 µg/mL) cells incubated with MTT show the formation of formazan crystals.

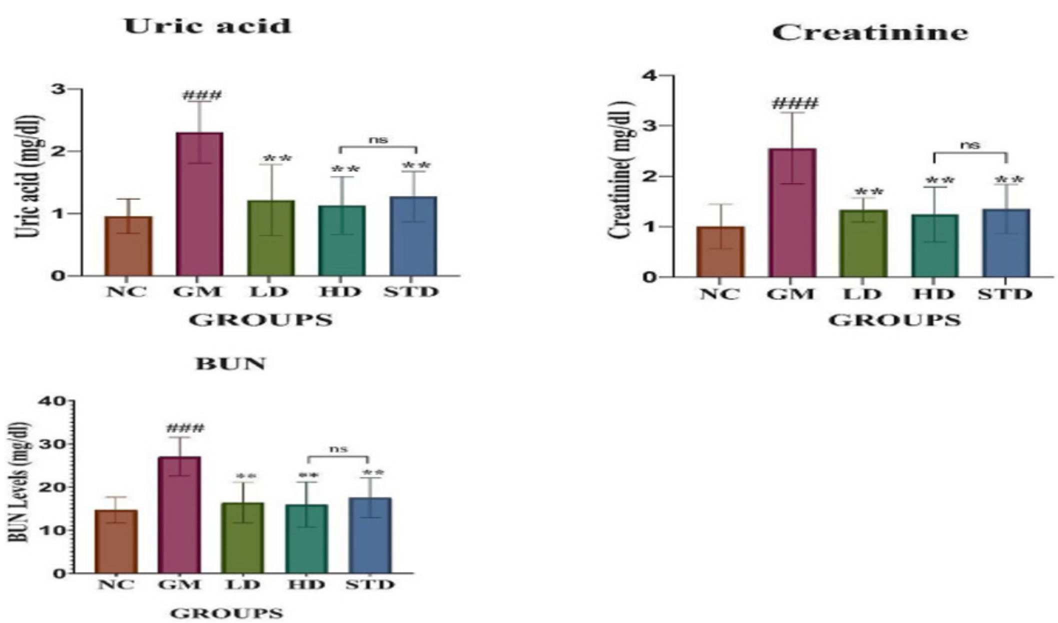

Figure 5: Effect of treatment of ELMC on a) Uric acid, b) Creatinine, c) BUN on GM induced nephrotoxicity in rats. NC: Normal control, GM: GM control, LD: Low dose, HD: High dose, STD: Standard. All data represented as Mean±SEM (n=6) ###p<0.001 vs normal control group, **p<0.05 vs GM group.

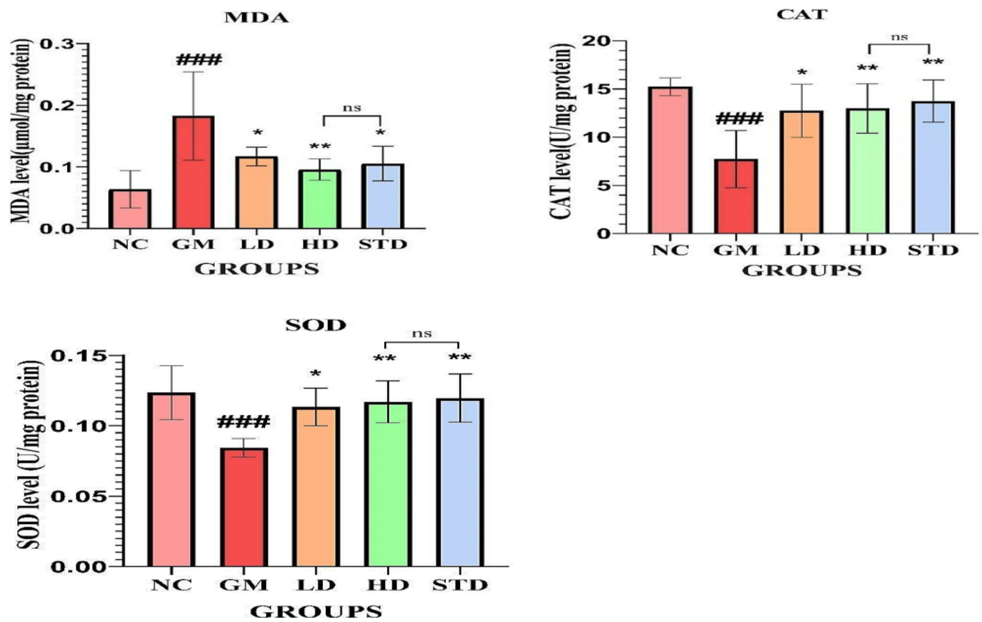

Figure 6: Effect of treatment of ELMC on a) MDA, b) CAT, c) SOD on GM induced nephrotoxicity in rats. NC: Normal control, GM: GM control, LD: Low dose, HD: High dose, STD: Standard. All data represented as Mean±SEM (*n*=6) ###*p*<0.001 vs normal control group, ***p*<0.05 vs GM group.

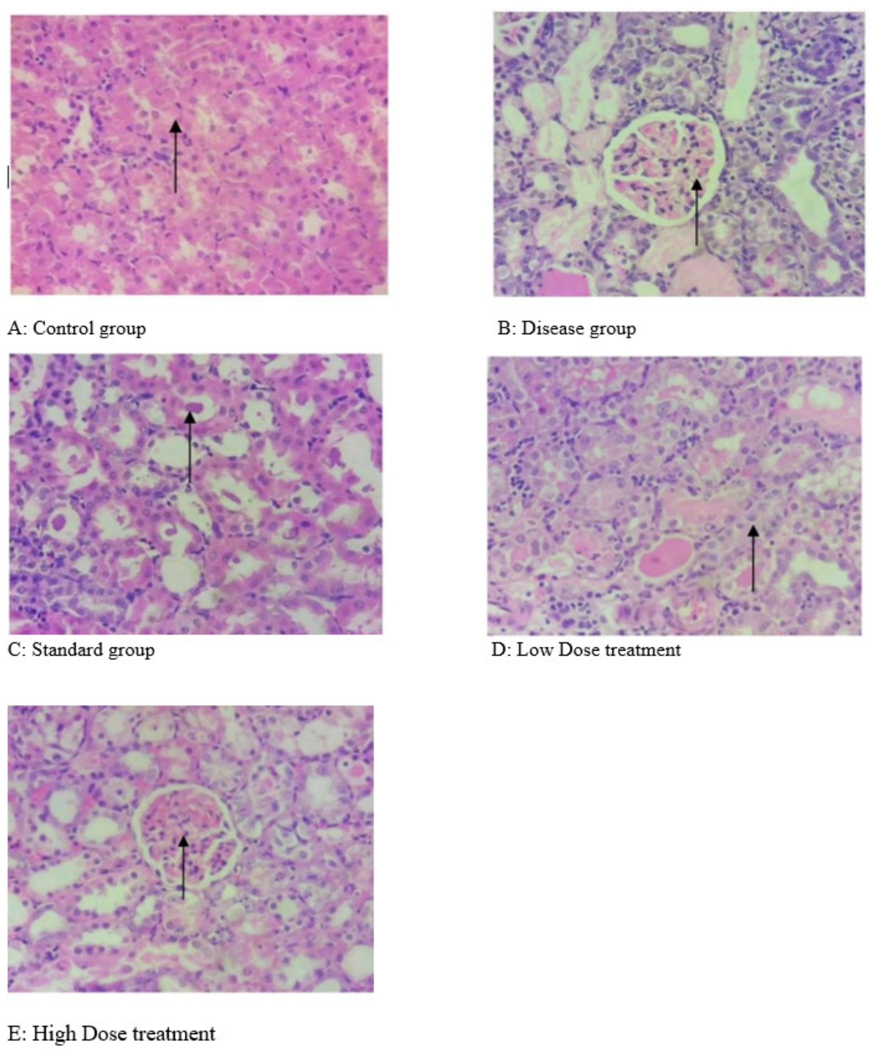

Figure 7: Histopathological study of kidney tissue.

function. Interestingly, no statistically significant differences were observed between the high-dose ELMC and standard treatment groups, indicating that ELMC may offer comparable nephroprotective efficacy.

Oxidative stress is a key mechanism underlying GM-induced nephrotoxicity, resulting from an imbalance between the generation of Reactive Oxygen Species (ROS) and the body's antioxidant defense system.[31] GM metabolism generates free radicals that damage proteins, lipids, and DNA, ultimately leading to cellular dysfunction and apoptosis.[32] Malondialdehyde (MDA), a byproduct of lipid peroxidation, is commonly used as a biomarker of oxidative stress.[33] Catalase (CAT) and Superoxide Dismutase (SOD) are essential enzymatic antioxidants that protect cells against ROS-mediated damage.[34] Consistent with previous studies, our results showed significantly increased MDA levels and decreased CAT and SOD activities in GM-treated rats.[30-35] Treatment with ELMC significantly reduced MDA levels and restored CAT and SOD activities in a dose-dependent manner (**p<0.05), indicating a strong antioxidant effect. These results suggest that ELMC mitigates oxidative damage and reinforces antioxidant defenses.

Histopathological evaluation further supported the biochemical findings. Consistent with earlier reports,[36,37] kidney tissues from GM-treated animals exhibited severe tubular degeneration, vascular congestion, and moderate interstitial inflammation. In contrast, the ELMC low-dose group showed mild interstitial inflammation, moderate tubular damage, and partial restoration of kidney architecture. The high-dose ELMC group demonstrated nearly normal renal histology, comparable to the standard treatment group, suggesting that ELMC provides significant protection against GM-induced renal injury.

CONCLUSION

The Ethanolic Leaf Extract of *Moringa concanensis* (ELMC) demonstrated significant *in vitro* antioxidant activity and was found to be non-cytotoxic in HEK 293 cells, indicating its safety for therapeutic application. *In vivo*, ELMC effectively attenuated gentamicin-induced nephrotoxicity by significantly reducing elevated serum levels of Blood Urea Nitrogen (BUN), creatinine, and uric acid. It also restored oxidative stress markers, as evidenced by decreased Malondialdehyde (MDA) levels and enhanced Catalase (CAT) and Superoxide Dismutase (SOD) activities. Histopathological examination further confirmed the nephroprotective effect, with the high-dose ELMC group (400 mg/kg) displaying renal architecture preservation comparable to that of the standard treatment group. These findings suggest that ELMC holds strong potential as a natural nephroprotective agent for the prevention and management of drug-induced renal injury, particularly gentamicin-associated nephrotoxicity.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

ABBREVIATIONS

ELMC: Ethanolic Leaves Extract of *Moringa concanensis*; **GM:** Gentamicin; **NC:** Normal Control; **LD:** Low Dose; **HD:** High Dose; **STD:** Standard; **MDA:** Malondialdehyde; **CAT:** Catalase; **SOD:** Superoxide Dismutase; **BUN:** Blood Urea Nitrogen; **DPPH:** 2,2-diphenyl-1-picrylhydrazyl; MTT: 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide; **HEK 293:** Human Embryonic Kidney 293 cells.

ETHICAL APPROVAL

Experimental procedures involving the animals adhered to the guidelines set forth by the Committee for the Purpose of Control and Supervision on Experiments on Animals (CPCSEA). Furthermore, the research protocol received approval from the Ethical Institutional Animal Ethical Committee with Reference no-(01/HP/2023).

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