Journal of Pharmaceutical Research International

33(46B): 168-179, 2021; Article no.JPRI.74062
ISSN: 2456-9119
(Past name: British Journal of Pharmaceutical Research, Past ISSN: 2231-2919, NLM ID: 101631759)

Nephroprotective Activity of *Sophora interrupta bedd.* against Gentamicin Induced Acute Renal Toxicity in Wistar Rats: An Experimental Study

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Authors' contributions

This work was carried out in collaboration between both authors. Both authors read and approved the final manuscript.

Article Information

DOI: 10.9734/JPRI/2021/v33i46B32929
Editor(s):
(1) Dr. Barkat Ali Khan, Gomal University, Pakistan.
Reviewers:
(1) Aashal Bhavesh Shah, GMERS Medical College, Valsad Veer Narmad South Gujarat University, India.
(2) Ahmed Salih Sahib, University of Kerbaba, Iraq.
Complete Peer review History: https://www.sdiarticle4.com/review-history/74062

Original Research Article

Received 20 July 2021
Accepted 27 September 2021
Published 21 October 2021

ABSTRACT

Background: Based on ayurvedic/folklore medicine majority of the medicinal plants are used for treatment of different ailments. *Sophora interrupta* as traditional medicine focused to do the research work for protection of renal injury.
Aim: The present study was investigated the nephroprotective activity of *Sophora interrupta* bedd. against gentamicin-induced acute renal toxicity in wistar rats.
Study Design Rats have received gentamicin (40 mg/kg) intraperitoneally (*i.p*.) once daily for 5 days of the study to induce nephrotoxicity along with test extract of *Sophora interrupta* bedd. at a dose of 200 &400 mg/kg, *p.o.* for 21 days. Urinary parameters like Creatinine, Urea, and Uric acid; Biochemical parameters like Alanine transaminase (ALT), Aspartate transaminase (AST), Lactate dehydrogenase (LDH), and Gamma Glutamyl Transferase (GGT), Creatinine, Total protein, and Albumin were measured along with tissue parameters and histopathological observations were carried out.
Results: The test extracts *Sophora interrupta* bedd. showed a prominent protective role against the gentamicin-induced nephrotoxicity with significant (*P*=.001) restoration in abnormal plasma & urine biomarkers as compared to the gentamicin-induced group. Treatment with both the doses (200 &

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400 mg/kg) of *Sophoria* extract showed significantly (*P*=.001; *P*=0.01) modified levels of antioxidant enzymes when compared to gentamicin-induced animals evidenced by structural restoration of the kidney.
Conclusion: These findings concluded that*, Sophora interrupta* bedd. exhibits a protective role against Gentamicin induced nephrotoxicity.

Keywords: Nephroprotective activity; Sophora interrupta bedd.; gentamicin and acute renal toxicity.

1. INTRODUCTION

Nephrotoxicity is a toxic effect due to drug overdosage on kidneys. The selective chemotherapeutic drugs including penicillins, cephalosporins, tetracyclines, sulfonamides, and aminoglycosides are likely to cause nephrotoxicity. The drug induced nephrotoxicity (DIN) is characterized by decreased urine concentrating capacity, tubular proteinuria, lysosomal enzymuria, mild glucosuria, decreased ammonium excretion, and lowering of glomerular filtration rate [1]. Gentamicin (GM) is an aminoglycoside antibiotic that shows a broad spectrum of chemotherapeutic activity and is particularly effective in severe sepsis. Its usage is limited because of severe adverse drug reactions (ADRs) like ototoxicity and nephrotoxicity. Nephrotoxicity has been related to a selective accumulation of drugs and their metabolic products in the renal cortex [2,3]. Approximately 8% to 26% of patients who received aminoglycosides for more than 7-10 days develop mild renal impairment which is almost reversible. DIN usually refers as gradual worsening of non oliguric renal failure and sometimes acute tubular necrosis may occur.

Sophora interrupta bedd. is a woody perennial shrub that belongs to the family Fabaceae. It grows endemically in seshachalam hill ranges in Tirumala, Chittoor district, A.P, India. More than 15 species in this genus have a long history of use in traditional Chinese medicine [4]. Several types of research and clinical practices, exhibited *invivo* and *invitro* experiments, have demonstrated that Sophora contains many phytoconstituents like matrine, oxymatrine type of alkaloids [5,6], flavonoids [7,8], saponins, and polysaccharides [9] which elute wide pharmacological actions, including anti-oxidant [10], anti-cancer [11], anti-asthmatic, anti-neoplastic, anti-microbial [12], anti-viral, anti-pyretic, cardiotonic, anti-inflammatory, diuretic and used in the treatment of eczema, colitis, and psoriasis [13]. The present was aimed to investigate the nephroprotective activity of *Sophora interrupta* bedd. against gentamicin-induced acute renal toxicity in wistar rats.

2. MATERIALS AND METHODS

Gentamicin was procured from Sigma Aldrich, USA. All the reagents were procured from Span diagnostics Ltd., Mumbai with high analytical grades.

2.1 Collection and Preparation of Plant Material

The plant material of *Sophora interrupta* Bedd.was collected and authenticated. The dried leaves of *Sophora interrupta* Bedd. were pulverized into coarse powder. The coarse powder was then subjected to continuous hot percolation in soxhlet apparatus with hydro alcohol and extracted till the solvent becomes colorless. The extract was evaporated under reduced pressure using a rotary evaporator at a temperature of 40ºC until the extract turns thick viscous syrupy and then the extract was transferred to an evaporating dish followed by drying at room temperature [14-16].

2.2 Experimental Procedure Animals

Twenty four healthy, male, Wistar albino rats, weighing 150-200gm grouped and housed in polypropylene cages maintained under standard laboratory conditions of alternating periods of light and darkness of 12 hours each, temperature (25±2ºC) and relative humidity (45 to 55%) was maintained. The rats free accessed to standard at pellet diet and tap water *ad libitum*.

2.2.1 Groups

The rats were randomly divided into four groups of six animals in each group. Group 1, healthy control rats or vehicle control administered with 0.9 % NaCl solution in a single oral dose of 2ml/kg/day for 21 days; Group 2, healthy rats received gentamicin (40 mg/kg) *i.p*. once daily for last 5 days of the study [17]; Group 3, rats

received a hydroalcoholic extract of *Sophora interrupta* bedd (HAESI) at a dose of 200 mg/kg, b.wt., per orally for 21 days and prior to that injection Gentamicin (40 mg/kg) was administered *i.p.* once daily for last 5 days; Group 4, rats received HAESI at a dose of 400 mg/kg, b.wt., per orally for 21 days and prior injection Gentamicin (40 mg/kg) was administered *i.p.* once daily for last 5 days.

2.3 Pharmacological Evaluation

2.3.1 Evaluation of urine and biochemical parameters

On the last day of the experimental period, the rats fasted overnight and blood samples were collected directly from the cardiac puncture of the sacrificed rats. The blood samples were kept at the temperature of 4ºC and centrifuged at 4000 rpm for 20 mins to collect the plasma samples. The plasma samples were used to estimate the biochemical parameters such as Alanine transaminase (ALT) [18], Aspartate Transaminase (ALT) [18], Lactate dehydrogenase (LDH) [19], and Gamma Glutamyl Transferase (GGT) [20, 21], Creatinine, Total protein and Albumin [23, 24].

Rats of each group were individually housed in metabolic cages for 24 h and urine was collected on the 21stday of the treatment. The Urine samples were used to estimate Creatinine [22], Urea [25, 26], and Uric acid [27].

2.3.2 Evaluation of antioxidant parameters and histopathological examination

Animals were sacrificed on the defined days, and immediately their kidneys were completely expelled, washed with saline, and instantly fixed in 10% buffered formalin medium. The kidneys were stored in formalin overnight. One kidney tissue was rinsed with 0.9% cold physiological saline and then homogenized with ice cold phosphate buffer (1:10 w/v) using a tissue homogenizer. The obtained homogenate was centrifuged at 800 rpm for 10 min at 4°C, the resulting supernatant was further centrifuged at 10500 rpm for 20 min at 4°C to yield the post mitochondrial supernatant. The said sample was used to determine the renal antioxidant like Superoxide dismutase (SOD), Catalase (CAT), Glutathione peroxidase (GPx) and Malondialdehyde (MDA) [29-33]. The stored kidney tissue of every globe was horizontally sectioned at about 2-3 mm thickness by the automatic tissue processor. All the sections were embedded in paraffin blocks separately, sections were cut at 5 µm by Leica 2BS Microtome and stained with hematoxylin and eosin (H&E). These sections were then examined under a light Microscope using 10 X & 40 X magnifications. The histopathological study was blinded to the treatment assignment of various study groups.

2.4 Statistical Analysis

All the data were expressed as Mean± Standard error mean (SEM). The difference between groups analysis was performed with one-way ANOVA followed by Dunnett's test using Graph Pad Prism Software.

3. RESULTS

3.1 Effect of *Sophoria* Extract on Plasma Biochemical Markers in Gentamicin Induced Nephrotoxicity Rat Model

Administration of Gentamicin caused a significant increase (*P*=.001) in biomarkers like ALT, AST, GGT, LDH, and Creatinine; while total protein (TP), albumin (Alb) were significantly (*P*=.001) decreased as compared to the vehicle treated animals. The elevated levels of ALT, AST, GGT, LDH and Creatinine leads to confirmation of gentamicin induced nephrotoxicity. However, treatment with 200 and 400 mg/kg of *Sophoria* extract resulted in significant (*P*=.001) restoration in altered biomarkers as compared to gentamicin induced animals thereby it confirms the protective effect of *Sophoria* extract (Table 1 and Graph 1-3).

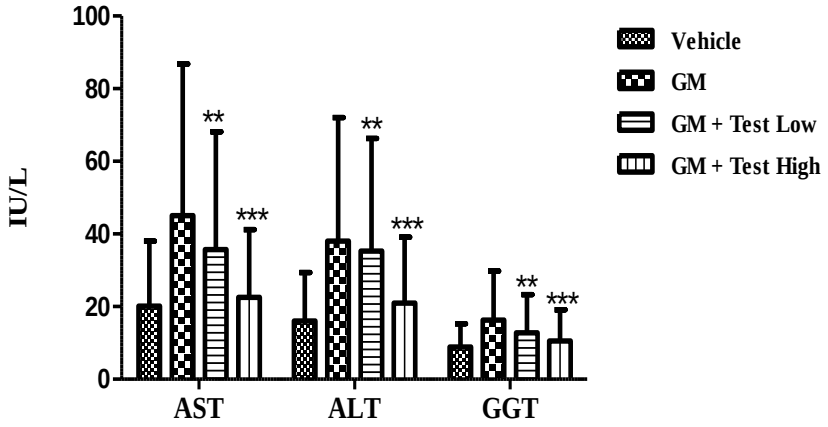
3.2 Effect of *Sophoria* Extract on Urinary Markers in Gentamicin Induced Nephrotoxicity Rat Model

Administration of Gentamicin resulted a significant (*P*=.001) alteration in kidney function biomarkers such as creatinine, urea, and uric acid as compared to the vehicle treated group. 21 days treatment with *Sophoria* extract 200 and 400 mg/kg resulted a significant (*P*=.001; *P*=.01) normalization of kidney function markers as compared to gentamicin induced group animals indicate that the protective effect of the extract against nephrotoxicity (Table 2 and Graph 4,5).

Table 1. Effect of *Sophoria* extract on plasma biochemical markers in Gentamicin induced Nephrotoxicity rat model

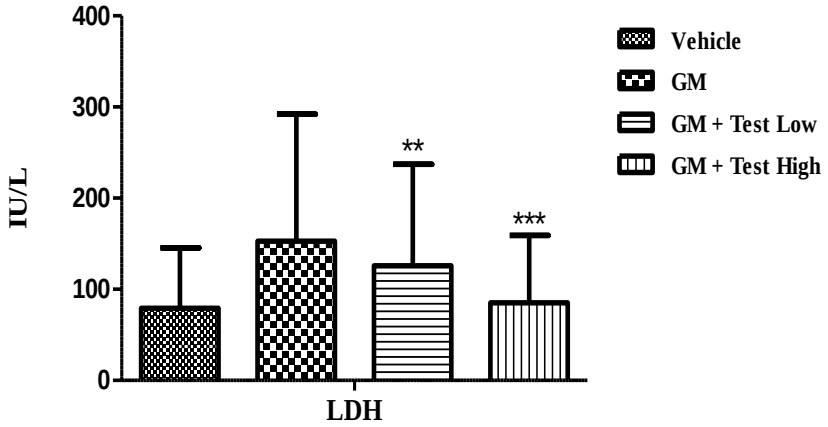
Parameter	Vehicle	GM	GM + HAESI 200mg/kg	GM + HAESI 400 mg/kg
AST (IU/L)	38.01 ± 2.21	86.75 ± 3.28	68.15 ± 3.33**	41.23± 3.80***
ALT (IU/L)	29.41 ± 2.71	72.02 ± 4.08	66.28 ± 4.33**	39.09 ± 2.81***
GGT (IU/L)	15.32 ± 2.44	29.83 ± 2.68	23.33 ± 2.31**	19.13 ± 1.87***
LDH (IU/L)	145.5 ± 12.94	292 ± 13.74	237.14 ± 14.49**	159.17 ±11.49***
Creatinine (mg/dl)	3.30 ± 0.83	11.36 ± 1.82	8.14 ± 1.72**	4.82 ± 1.63***
Total Protien (mg/dl)	6.34 ± 1.83	1.26 ± 0.36	3.24 ± 1.12**	5.92 ± 1.45***
Albumin (g/dl)	3.62 ± 0.82	1.36 ± 0.42	2.14 ± 0.72**	3.23 ± 0.83***

Data was expressed as Mean ± SEM. Treatment groups were compared with GM control
**P< 0.05; **P< 0.01; ***P< 0.001 using one-way ANOVA with Dunnett's test.*



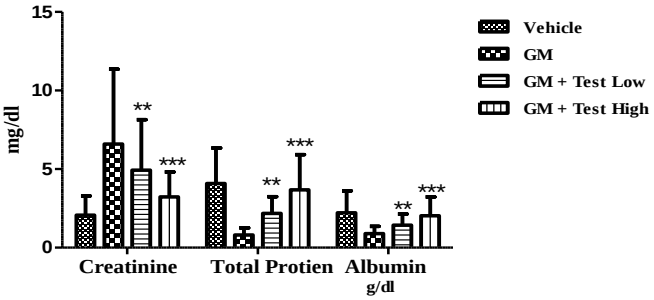
Graph 1. Effect of *Sophoria* extract on plasma biochemical markers (AST, ALT, GGT) in Gentamicin induced Nephrotoxicity rat model

Data was expressed as Mean ± SEM. Treatment groups were compared with GM control
P< 0.05; **P< 0.01;*P< 0.001 using one-way ANOVA with Dunnett's test.*



Graph 2. Effect of *Sophoria* extract on plasma Lactate Dehydrogenase levels in Gentamicin induced Nephrotoxicity rat model

Data was expressed as Mean ± SEM. Treatment groups were compared with GM control
p < 0.05; **p < 0.01;*p< 0.001 using one-way ANOVA with Dunnett's test.*



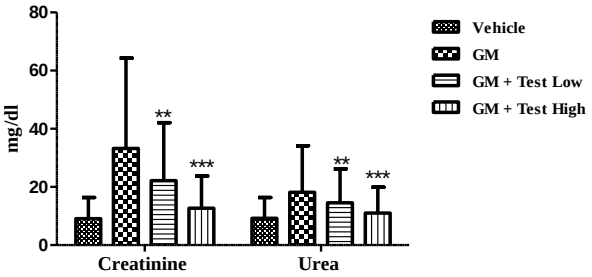
Graph 3. Effect of *Sophoria* extract on plasma biochemical markers (Creatinine, Total Protien, and Albumin) in Gentamicin induced Nephrotoxicity rat model

Data was expressed as Mean ± SEM. Treatment groups were compared with GM control
**P< 0.05; **P< 0.01; ***P< 0.001 using one-way ANOVA with Dunnett's test.*

Table 2. Effect of *Sophoria* extract on Urinary markers in Gentamicin induced Nephrotoxicity rat model

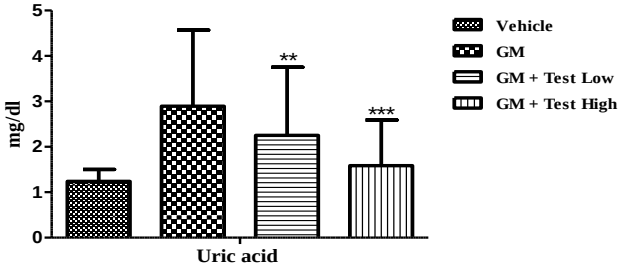
Parameter	Vehicle	GM	GM + HAESI 200mg/kg	GM + HAESI 400mg/kg
Creatinine (mg/dl)	16.36 ± 1.82	64.30 ± 2.23	42.1 ± 2.17**	23.8 ± 1.62***
Uric acid (mg/dl)	1.50 ± 0.98	4.57 ± 1.22	3.75 ± 0.75**	2.59 ± 0.58***
Urea (mg/dl)	16.37 ± 2.14	34.18 ± 2.13	26.23 ± 2.96**	19.92 ± 2.15***

Data was expressed as Mean ± SEM. Treatment groups were compared with GM control
**P< 0.05; **P< 0.01; ***P< 0.001 using one-way ANOVA with Dunnett's test*



Graph 4. Effect of *Sophoria* extract on UrinaryCreatinine & Urea levels in Gentamicin induced Nephrotoxicity rat model

Data was expressed as Mean ± SEM. Treatment groups were compared with GM control
**P< 0.05; **P< 0.01; ***P< 0.001 using one-way ANOVA with Dunnett's test*



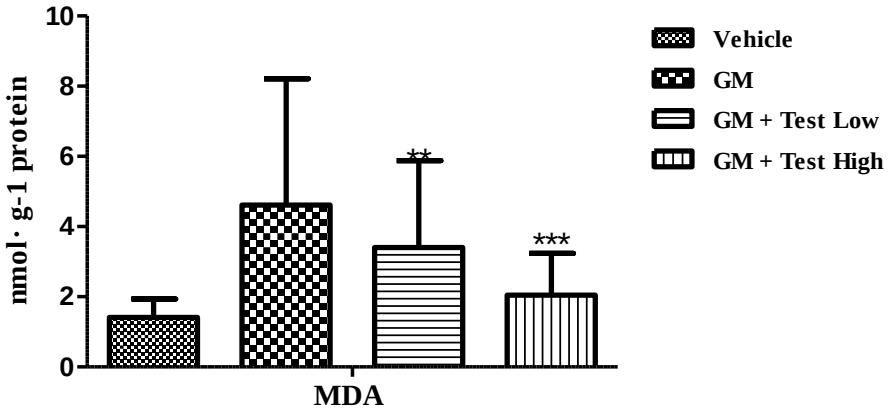
Graph 5. Effect of *Sophoria* extract on UrinaryUric Acid levels in Gentamicin induced Nephrotoxicity rat model

Data was expressed as Mean ± SEM. Treatment groups were compared with GM control
**P< 0.05; **P< 0.01; ***P< 0.001 using one-way ANOVA with Dunnett's test.*

Table 3. Effect of *Sophoria* extract on tissue parameters in Gentamicin induced Nephrotoxicity rat model

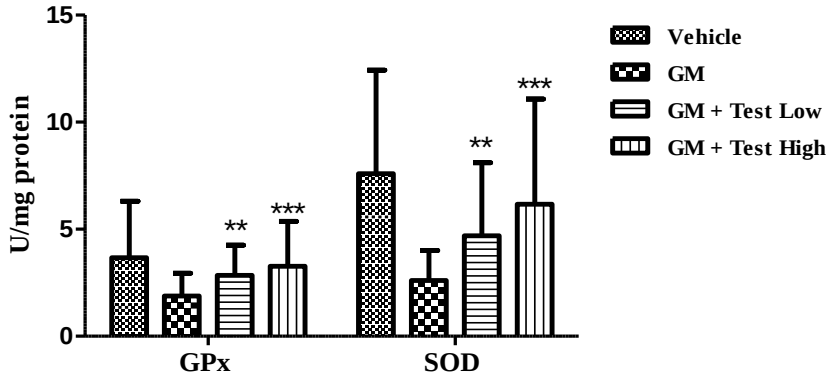
Parameter	Vehicle	GM	GM + HAESI 200 mg/kg	GM + HAESI 400mg/kg
MDA (nmol· g−1 protein)	1.94 ± 0.88	8.21 ± 1.02	5.88 ± 0.92**	3.24 ± 0.86***
SOD (U/mg protein)	12.43±2.76	4.01 ± 1.19	8.11 ± 1.28**	11.08 ± 1.25***
CAT (U/mg of protein)	36.90± 2.37	16.86 ± 1.93	26.15 ± 2.67**	33.21 ± 2.49***
GPx (U/mg of protein)	6.31 ± 1.03	2.94 ± 0.82	4.25 ± 1.43**	5.37 ± 1.18***

Data was expressed as Mean ± SEM. Treatment groups were compared with GM control
***P< 0.05; **P< 0.01; ***P< 0.001 using one-way ANOVA with Dunnett's test.*



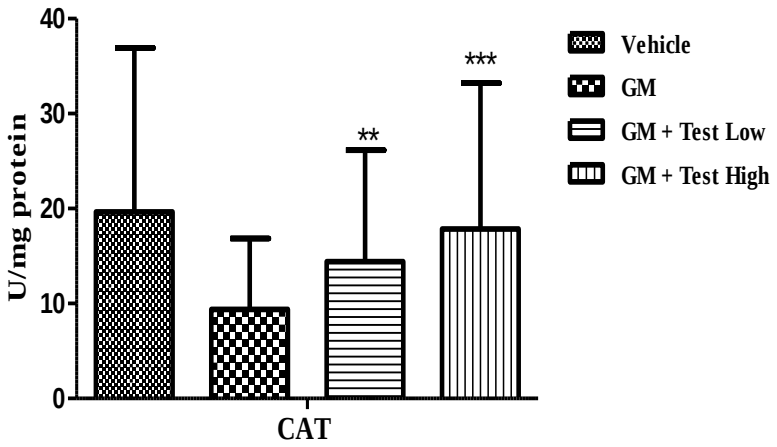
Graph 6. Effect of *Sophoria* extract on tissue MDA levels in Gentamicin induced Nephrotoxicity rat model

Data was expressed as Mean ± SEM. Treatment groups were compared with GM control
***P< 0.05; **P< 0.01; ***P< 0.001 using one-way ANOVA with Dunnett's test.*



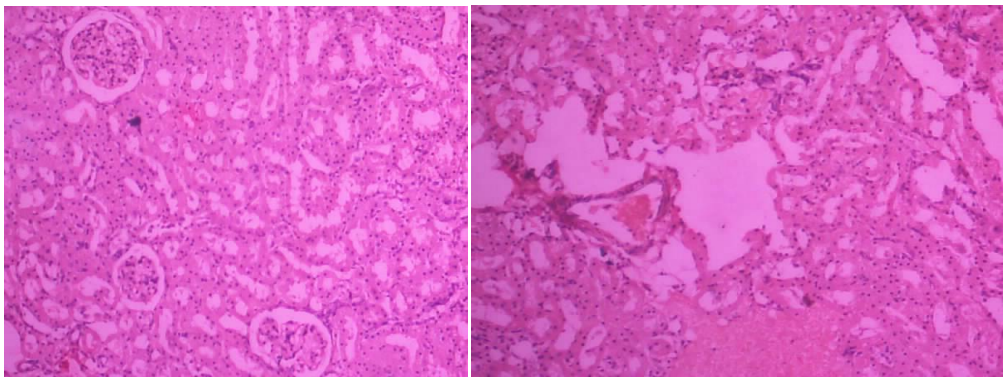
Graph 7. Effect of *Sophoria* extract on tissue anti-oxidants (GPx, SOD) in Gentamicin induced Nephrotoxicity rat model

Data was expressed as Mean ± SEM. Treatment groups were compared with GM control
**P< 0.05; **P< 0.01; ***P< 0.001 using one-way ANOVA with Dunnett's test.*

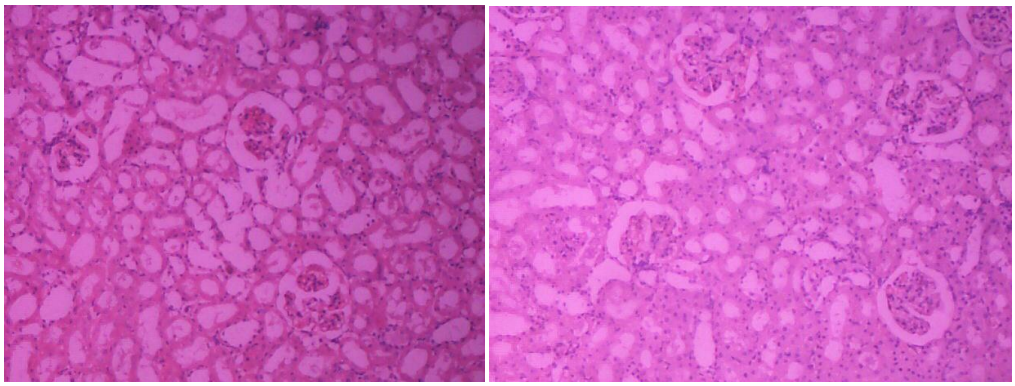


Graph 8. Effect of *Sophoria* extract on tissue anti-oxidant (Catalase) in Gentamicin induced Nephrotoxicity rat model

Data was expressed as Mean ± SEM. Treatment groups were compared with GM control
**P< 0.05; **P< 0.01; ***P< 0.001 using one-way ANOVA with Dunnett's test.*



Vehicle control showing normal morphological view of renal sections
GM treated group showed the degeneration, necrosis in tubules and swelling in glomerulus



Group treated with *Sophoria* 200 mg/kg showed slight tubular degenerative and necrotic changes
Animal treated with *Sophoria* 400 mgj/kg showed regeneration in tubular epithelial cells.

Plate 1. Histopathological examinations

3.3 Effect of *Sophoria* Extract on Tissue Parameters in Gentamicin Induced Nephrotoxicity Rat Model

Gentamicin challenged rats exhibited a significant (*P*=.001) elevation of tissue MDA levels (a lipid peroxidation marker) while significant (*P*=.001) reduction in tissue antioxidants like SOD, CAT & GPx as compared to vehicle treated rats. Treatment with *Sophoria* extract for 21 days was shown significantly (*P*=.001; *P*=.01) restored the levels of endogenous antioxidants as compared to Gentamicin induced animals (Table 3 and Graph 6-8).

3.4 Histopathological Outcomes

The histopathological examinations of the kidney shown normal architecture of renal tubules, endothelium, and non-inflammatory cell infiltration within the interstitium in the vehicle treated animals. The gentamicin (Group-II) induced animals shown marked tubular dilation, extensive epithelial necrosis, and denudation of the epithelium, tubular cast formation, dystrophic mineralization, epithelial regeneration, and mild neutrophil infiltration at the level of the renal convoluted tubules, affecting more than 60% of the epithelial necrosis. The small blood vessels were multifocally affected by endothelial swelling, necrosis, and occasional thrombosis. The tubule interstitial space was distended by congestion, edema and mixed inflammatory infiltrates, affecting less than 25% of renal tissue [34].

The histological changes of renal tissues from treated rats with *Sophoria* extract (200 mg/kg) contain multifocal epithelial coagulative necrosis, cast formation, thickening of the renal tubular basement membrane, vascular endothelial cell swelling, mild interstitial congestion, edema, multifocal mixed inflammatory infiltrates and affecting less than 60% of renal tublules. The glomeruli showed no significant changes. The renal tissue of treated rats with *Sophoria* extract (400 mg/kg) showed loss of brush border, mild vacuolar (hydropic) degeneration, and occasional individual cell necrosis of the proximal renal tubular epithelium, affecting less than 25% of tubular cells. No significant histological changes of the endothelial, glomerular, and interstitial components were identified. Overall, gentamicin induced nephrotoxicity renal tissue significantly increased the injuries of tubular, endothelial, and tubule interstitial changes compared to the vehicle treated aimals. Treatment of *Sophoria* extract tissues exhibited dose dependent protection against gentamicin induced renal damages.

4. DISCUSSION

Nephrotoxicity is undesirable ADRs of chemotherapeutic agents in general. Most chemotherapy drugs targets pathways and are essential to dividing cells [35]. Several studies have now documented the importance of reactive oxygen metabolites in gentamicin induced renal damage [36]. Nephrotoxicity of the drugs is usually associated with their accumulation in the renal cortex, dependent upon their affinity to kidneys and on the kinetics of the drug trapping process [37]. The nephrotoxicity of aminoglycoside antibiotics, and especially that of the most commonly used compound, gentamicin, is well established [38,39].

In the current study, nephrotoxicity was induced by gentamicin is a commonly used experimental model for evaluation of the nephroprotective activity of the drugs. Nephrotoxicity is rapidly induced in rats and marked with established morphological changes and biochemical markers. High doses (40 mg/kg or more for gentamicin) are necessary for animals to rapidly induce extended cortical necrosis and overt renal dysfunction [40].

Gentamicin (GM), belonging to the aminoglycoside group of antimicrobial agents, actively concentrated in the renal cortex and proximal tubular cells. GM, after entering the cortical cells it binds to lysosomes with the formation of myeloid bodies/secondary lysosomes thus impairing mitochondrial function, interfering with the tubular transport, increasing oxidative stress, and forming free radicals which are associated with increase in lipid peroxidation and decrease in antioxidant enzyme activity in the kidney resulting in renal toxicity [41-43].

In the current study, gentamicin induction caused elevation in the measured biochemical parameters such as AST, ALT, LDH, GGT levels that could be attributed to an increased catabolic state of the rats due to the prolonged anorexia and change in the permeability of hepatocyte membrane which was compared to the vehicle treated rats. Elevation of creatinine levels in plasma was taken as the index of nephrotoxicity [44-46]. Gentamicin induction caused depletion in total protein and albumin levels that might be

depressed as a result of defective protein synthesis. Pre-treatment with *Sophoria* extract at both dose levels (200 mg/kg & 400 mg/kg) significantly reduced the elevated levels of plasma biochemical parameters indicating the nephroprotective activity.

Administration of the Gentamicin in rats caused renal dysfunction and diminished glomerular filtration rate, resulted a reduction of the kidney's ability to filter creatinine and the non-protein waste product is produced. Moreover, during renal dysfunction, the levels of urea and uric acid are elevated this might be a sensitive indicator of tubular damage [47,48]. Test extract treatment significantly restored the altered urinary parameters.

Oxidative stress plays a central role in gentamicin induced renal physiopathology and is likely to cause cellular lesions and necrosis of the kidneys [49]. Several studies previously carried out have shown the key role of free radicals in lipid peroxidation and antioxidant enzymes such as superoxide dismutase and catalase in counteracting their actions [50]. SOD, CAT, and GPx are antioxidant enzymes will neutralize free radicals and considered as cellular defense barriers against oxidative stress [49]. The results of the present study showed the administration of gentamicin significantly increased MDA levels and depletion of CAT, SOD, and GPx levels. Administration of *Sophoria* extract with 200 mg/kg, 400 mg/kg significantly reduced the elevation of MDA levels and accelerated the antioxidant defense enzymes comparable to gentamicin induced animals. Thereby the antioxidant activity of *Sophoria* extract was confirmed and the results suggested that the exhibition of antioxidant property contributing to its nephroprotective activity [51].

The histological investigation of kidneys from rats induced with gentamicin showed hypercellularity in mesangial cells and proliferative glomerulonephritis with degeneration of renal tubular epithelium when compared to the vehicle treated rats. However, pre-treatment with the test extract of *Sophoria*at both dose levels (200 & 400 mg/kg, b.wt.,) restored the degenerated architecture of the renal tubular epithelium indicating the protective effect of the test extract with free radical scavenging activity.

The different therapeutic agents are adversely affecting kidneys resulting in acute renal failure, chronic interstitial nephritis, and nephrotic syndrome because of an increasing number of usage potent therapeutic drugs like aminoglycoside antibiotics, chemotherapeutic agents, and NSAIDs. Exposure to chemical reagents like ethylene glycol, carbon tetrachloride, sodium oxalate, and heavy metal like lead, mercury, arsenic, and cadmium also induces nephrotoxicity. Prompt recognition of disease and cessation of the responsible drug is usually the only necessary therapy. Nephroprotective agents are substances that possess protective activity against nephrotoxicity. Medicinal plants have curative properties due to the presence of various complex chemical substances [52].

5. CONCLUSION

Aminoglycosides have long been identified as one of the commonest causes of drug induced nephrotoxicity. In the current study, Gentamicin was used to induce nephrotoxicity in rats and was evaluated for the nephroprotective activity with pre-treatment of test extract of *Sophoria* at graded doses (200 & 400 mg/kg). Upon induction with GM, there is an alteration in the plasma biochemical markers such as AST, ALT, LDH, GGT, Creatinine, Total protein and Albumin levels, Urinary parameters such as Urinary Creatinine, Urea, Uric acid levels, tissue anti-oxidant levels such as SOD, CAT, GPx, and tissue pro-oxidant MDA levels. However, pre-treatment with test extract of *Sophoria* significantly restored the altered parameters exhibiting the protective activity through anti-oxidant activity.

DISCLAIMER

The products used for this research are commonly and predominantly use products in our area of research and country. There is absolutely no conflict of interest between the authors and producers of the products because we do not intend to use these products as an avenue for any litigation but for the advancement of knowledge. Also, the research was not funded by the producing company rather it was funded by personal efforts of the authors.

CONTENT

It is not applicable.

ETHICAL APPROVAL

The experimental protocol was designed as per the guidelines of the Institutional Animal Ethic

Committee (IAEC) which is certified by the Committee for the Purpose of Control and Supervision of Experiments on Animals (CPCSEA), India (1995/PO/Re/S/17/CPCSEA).

STUDY SIGNIFICANCE

The study highlights the efficacy of "ayurvedic/folklore" which is an ancient tradition, used in some parts of India. This ancient concept should be carefully evaluated in the light of modern medical science and can be utilized partially if found suitable.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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