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The Nephroprotective Activity of *Elephantopus scaber* Linn Roots, Leaves, and Flowers on Gentamicin Induced Nephrotoxicity

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ABSTRACT

The goal of the current investigation was to determine whether an ethanolic extract of *Elephantopus scaber* had nephroprotective properties. Animals into five groups, including Group I control, Group ii negative control, that also started to receive Gentamicin 100mg/kg B.W., i. p, O. D. For 12 days, For 12 days, Group iii began to receive a kind *Elephantopus scaber* extract of the roots. Group IV received a section of the flowers. Group III received an *Elephantopus scaber* extract of the sources, and Group IV received an *Elephantopus scaber* extract of the flowers. Gentamicin 100mg/kg, i.p., O.D. plus *Elephantopus scaber* leaf extract, 100mg/kg B.W., was administered to Group V for 12 days. It also tested the in vitro antioxidant and free radical scavenging operations of various extracts Nephrotoxicity associated with gentamicin. Overall study findings indicated that *Elephantopus scaber* root extract successfully prevents kidney damage brought on besides gentamicin-induced Nephrotoxicity while also going to lower physiochemical urinary but also serum marker enzymatic as though creatinine, urea, but also uric acid. In gentamicin-treated animals, the kidney histopathology examinations found that *Elephantopus scaber* root extract had a protective effect. The findings showed that pretreatment with an ethanolic extract of *Elephantopus scaber* roots might help avoid kidney injury in experimental mice caused by gentamicin.

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INTRODUCTION

A kidney malfunction is Nephrotoxicity and results from exposure to outside factors such as medications, poisons, and environmental pollutants. Numerous medicinal substances have been demonstrated to cause Nephrotoxicity with clinical significance [1]. Antibiotics with aminoglycosides are frequently used to treat gram-negative infections. However, the main drawbacks in clinical practice are Nephrotoxicity and ototoxicity. Neomycin, gentamicin, and tobramycin are said to rank in order of Nephrotoxicity among the several aminoglycosides. The feared gram-negative infections are typi-

cally treated with gentamicin, a core aminoglycoside antibiotic. About 15–30% of gentamicin-treated patients experience Nephrotoxicity [2]. Many interrelated routes are involved in gentamicin's absorption, distribution, metabolism, and excretion. Free radicals and reactive oxygen species are produced from lipid peroxidation caused by gentamicin, which is highly toxic to nearby tissues and is the primary etiological element inside gentamicin-induced Nephrotoxicity's pathobiology [3].

Caused by gentamicin-tubular necrosis is primarily limited to the proximal tubule and serves as an example of nephrotoxicity and kidney injury [4]. Although the underlying pathophysiology of gentamicin nephrotoxicity seems to be unknown, that natural substance must have been shown to increase the production of oxidative stress or reactive oxygen species in vivo and in vitro studies. Increased production of reactive oxygen species is believed complete contribute there in etiology of some xenobiotic toxicity because it can harm a variety of macromolecules [5], induce serious epithelial injuries but instead tissue damage through some combination of systems, which would include peroxidation like membrane lipids, protein denaturation, as well as D.N.A. damage [6].

Naturally occurring herbal treatments have been the mainstay of primary healthcare for a long time. Plants have been a rich source of practical and secure medicines since the beginning. We discovered that the *Elephantopus scaber* L. (Asteraceae) is a common medicinal plant used by the Zhuang people in Jingxi County of Southwest China between 2008 and 2012 during its dragon-boat festival, which occurs within the fifth month of something like the china lunar calendar and also has a background of well over 700 years. There are roughly 30 species in the Elephantopus, most of which are located in South America. Only two species, *E. scaber* and *E. tomentosus*, are native to Southwest China [7]. *E. scaber* is usually used by municipal Zhuang individuals as just a herbal remedy to treat various illnesses, such as headaches, colds, diarrhea, hepatitis, and bronchitis. Thirty substances, including four sesquiterpene lactones, nine triterpenes, and five flavones, have been identified in *E. scaber*. The extracts or chemicals from this species contain antibiosis, antiviral, and cytotoxicity capabilities, according to past evolved in such a way experiments through *E. scaber* [8]. Sesquiterpene lactones have been explicitly evaluated for their hepatoprotective and anti-inflammatory properties, which helped partially validate earlier theories about *E. scaber*.

Most current therapies are palliative, emphasizing symptom management above prevention or cure. Creating efficient treatments for these crippling neurological conditions is the aim of N.D.D. research. We have done a screen to look at the neuroprotective potential of natural compounds to find new therapeutic targets. Among the compounds identified was *Elephantopus scaber*, a shrub endemic to tropical Africa. Our studies showed that *E. scaber* significantly decreased oxidative stress in cells expressing increased cellular viability [9].

Further study revealed that *E. scaber* reduced reactive oxygen species (R.O.S.) production, increased expression of antioxidant enzymes, and decreased caspase-3 activation. These results suggest that *E. scaber* may protect against N.D.D.s by its antioxidant and anti-apoptotic effects [10]. Elephantopus scaber is already preferred even as a factory to determine scientific information considering the Nephroprotective work properly as there are hardly accepted scientific news stories of just this tree's Nephroprotective activity. The current study's objective is to assess Elephantopus scaber root, flower, and leaf extract's ability to protect the kidneys against gentamicin-induced Nephrotoxicity in experimental mice [11].

MATERIALS AND METHODS

Collection and Authentication of Plant

In January, residents collected the leaves, flowers, and roots of the *Elephantopus scaber*. Individual plant pieces were collected and authenticated in a herbarium file.

Extraction of Plant Material

Elephantopus scaber leaves, flowers, and roots were dried individually in a lab at room temperature. After drying, roots, flowers, and leaves were ground into a coarse powder. To preserve consistency, that whole granular particle of leaf surface, flower petals, but instead, origins had been kept through sieve no [12]. Eighteen before even being situated along ordinary person glass jars but instead managed to keep in some relaxed, dry environment for the other physical-chemical science but rather removal. Using a soxhlet apparatus, 200 g of coarsely ground leaf, flower, and root powder was extracted with ethanol for 36 hours to remove any remaining fatty materials. Once the extraction process was complete, the extract was obtained but centered together in a vacuum environment. The relevant extracts' percentage yield was computed in the pressure drop that used a rotary flash evaporator [13]. The dried crude extract was then kept at 2 to 8^{o}C in an airtight con-

tainer for future research.

Elephantopus scaber Leaves, Flowers, and Roots Powder Physicochemical Analysis

Using accepted methods, thickly hardened particles anyway contain relevant scaber leaves, flowers, but also root systems must have been assessed for a variety of physical-chemical properties, along with destruction forward dryers, total ash actual worth, hydrochloric inert ash benefit, highly soluble in water ash benefit, or foaming index [14].

Phyto-Chemical Analysis of *Elephantopus scaber* Leaves, Flowers, and Roots Powder Ethanolic Extract

The ethanolic quote has been exposed complete quantifiable synthetic exploration for the identity of the phytoconstituents somewhere around flavonoids, alkaloids, glycosides, carbohydrates, triterpenoids, phytosterols, but rather tannins [15].

Antioxidant Activity of Different Extracts by DPPH Method

Preparation of Standard Solution

The necessary amount of ascorbic acid was dissolved in methanol to give the concentrations of 100, 200, 300, 400, and 500 μg/ml.

Preparation of Specified Test

Standard stock solution of extracts seems to be made by mixing 100 mg from each of the three fluid samples, such as 100 ml of methanol, to accomplish one concentration of 1 mg/ml. One per puppet has been prepared by diluting to either an accumulation of 100, 200, 300, 400, or 500 μg/ml in a 10 ml volumetric flask.

Preparation of DPPH Solution

The DPPH solution was made by dissolving 4.3 mg of DPPH in 3.3 ml of methanol and shielding it from light by wrapping aluminum foil around the test tubes.

Protocol for Estimation of DPPH Scavenging Activity

3 ml of methanol was added to 150 μl of DPPH solution, and an instantaneous absorbance measurement was made at 516 nm for the control reading. Methanol was used to dilute the test sample up to 3 ml. The tube was added 150 μl of the DPPH solution to each test. After 15 minutes, the UV-visible spectrophotometer (Systronic) was used to quantify an absorption at 516 nm and use methanol as a blank. Using the following equation, its free radical scavenging activity (% antiradical activity) must have been determined:

$$\%Antiradical\ \ Activity = \frac{Control\ Absorbance - Sample\ Absorbance}{Control\ Absorbance} \times 100$$

Preparation of Extracts Formulation

For additional in-vivo research, a suspension preparation of the ethanolic section of Elephantopus scaber leaves and flowers but roots must have been designed and synthesized separately out of 0.5% C.M.C. solution.

In Vivo Pharmacological Study

Animal Care and Handling

Wistar albino rats, sexed and weighing 140 and 200gm, were used for the experiment. They were fed a standard pallet diet and were given access to water as needed throughout the investigation. Wildlife had been acclimated to a characteristic feature research lab requirements in such cross-ventilated animal care with the temperature of 25°c, the one relative humidity like 44-56%, but rather 12-hour cycles of light as well as darkness. According to CPCSEA norms [16], the investigation received approval from the institutional ethics committee.

Acute Toxicity Study of Extracts

On Wistar albino rats, a sensitive oral toxicity assessment was assessed by OECD norms (425). Rats were starved overnight before the experiment. The animals were put into three groups of three each. All three of the animals in the first team received one injection of 2000mg/kg of just an ethanolic extract made out of*Elephantopus scaber* leaves, flowers, and roots, while the three animals in the second Group received a dose of 2000mg/kg of an ethanolic extract made from *Elephantopus scaber* flowers. The three animals in the third Group received a dose of 2000mg/kg of an ethanolic extract made from *Elephantopus scaber* leaves and roots by gavage using an oral cannula [17]. After 24 hours after medication, all animals from all groups were individually examined for any significant indicators of toxicity, such as convulsions, tremors, circling, depression, and mortality. Special attention was paid to the initial 4 hours and the next 24 hours. Since no fatalities were discovered, the administered amount was deemed tolerable. The highest safe dose of such an ethanolic extract after all Elephantopus scaber leaves, flowers, and roots was 2000mg/kg.

In-Vivo Nephroprotective Activity in Gentamicin-Induced Nephrotoxicity

Grouping and Treatment of the Animals

The animals seemed to be categorized into five equivalent clusters completely at random such as six rats, all as continues to follow:

Group I, Control: only vehicle-treated

Group II, Negative Control: Gentamicin 100 mg/kg B.W., i.p, O.D. for 12 days

Group III, Test group I: received roots extract of *Elephantopus scaber*, 100mg/kg B.W., p.o. + gentamicin 100 mg/kg, i.p, O.D. for 12 days

Group IV, Test group II: received flowers extract of *Elephantopus scaber*, 100mg/kg B.W., p.o. + gentamicin 100mg/kg, i.p, O.D. for 12 days

Group V, Test group III: received leaves extract of *Elephantopus scaber*, 100mg/kg B.W., p.o. + gentamicin 100mg/kg, i.p, O.D. for 12 days

The 100mg/kg/day of gentamicin was transfused intra-peritoneally for 12 days. Well, as helps in extracting seemed to be administered to the patient verbally through gavage nearly every day, 1 hour before actually gentamicin intravenous such as 12 days [18].

Evaluation of Nephroprotective Activity in Gentamicin-Induced Nephrotoxicity

All animals had their initial weight measured at the beginning of the investigation (day 0), and their final Strength training was gone just as a result of both the test (at the end of the study, i.e., 12 days). To collect 24-hour urine after the final gentamicin dose, all the animals were housed in groups of two in metabolic cages. Water was available to animals at all times when pee was being collected. The urine was prepared by adding a drop of strong hydrochloric acid. Then it was kept at 40°C and used to estimate several biochemical parameters, such as serum creatinine, urea, and uric acid, as a sign of glomerular damage. A digital pH meter was used to measure the volume (in milliliters) and pH of the collected urine the following day [19].

Following urine collection, animals from all groups had retro-orbital punctures performed under light ether anesthesia to gather blood. To analyze serum, blood seems to be authorized by about institutional framework such as 45 minutes at room temperature. But using a trying-to-cool centrifuge, blood collected appeared to be isolated besides emulsification about as 100rpm as well as 4^0c such as 15 minutes. A different face cream was used to estimate numerous physicochemical markers, such as serum creatinine, urea, and uric acid, as little more than a pointer sure glomerular pain. One living creature of each band must have been sacrificed along a set of rules that defines displacements after the study after urine and blood samples had been taken from all groups of animals. The abdomen had been opened, and the left kidneys had been removed and repaired such as 10% formalin solution. A solved kidney had been cut into slices roughly 1mm thick using a microtome, and after the tissue had been processed, paraffin segments (5-μm thickness) seemed to be made. Histological slides were then created and stained with hematoxylin and eosin (H&E) for histopathological analysis under a light microscope.

Biochemical Analysis on Collected Samples of Urine and Serum

Utilizing a double beam U.V./Visible spectrophotometer, biochemical parameters on urine and serum samples were spectrophotometrically evaluated (UV-Visible spectrophotometer). Using related Auto span diagnostic kits, it and estimation after all plasma creatinine, urea, and uric acid even as an indicator of glomerular damage [20].

Statistical Analysis

Using the statistical program Graph Pad, In-Stat 3, all the values are expressed as the mean, standard error of the mean, and examined for ANOVA and posthoc Tukey-Kramer Multiple Comparisons Test. At $P< 0.05$ levels, differences across groups were deemed significant.

RESULTS AND DISCUSSION

In experimental research, gentamicin-induced organ damage has been commonly utilized because an animal model to ascertain severe renal failure and reactive species has been posited as the essential core in methodologies the said obviously lead of about tubing necrosis and just a drop through glomerular filtration rate.

Oxidative stress has been hypothesized to provide a conclusion in the pathophysiology of gentamicin-induced Nephrotoxicity. It is possible to suppose that the primary causes of gentamicin-induced Nephrotoxicity are the induction of oxidative stress and inflammation, amplification of harm, or a reference between the methodologies behind adjusts of the tubules and glomeruli.

In gentamicin-induced Nephrotoxicity, significant increases in serum creatinine and urea concentration were postulated as significant intentional kidney damage. When it comes to the beginning etiology of kidney disease, serum creatinine concentration is a more robust marker than urea.

According to several studies, oxygen free radicals are essential mediators of gentamicin-induced acute renal failure (A.R.F.). Additionally, immediately following parenchymal damage, urea concentrations start to rise.

Therefore, using formulations with antioxidant characteristics is a critical strategy to reduce gentamicin-induced Nephrotoxicity.

Table 1: Physiochemical Analysis of Powder of *Elephantopus scaber* Roots, Leaves & Flowers

Parameters	Observation (%)		
	Roots	Leaves	Flowers
Loss on drying	0.8	0.5	0.4
Total ash value	9	8.5	8
Acid insoluble ash value	2.9	3.2	2.8
Acid insoluble ash value	1.39	1.98	1.87
Foaming index	19 ml	17 ml	14 ml

Table 2: Phytochemical Screening of Ethanolic Extract of *Elephantopus scaber* Roots, Leaves & Flowers

Chemical constituents	Ethanolic extract of E.S. Roots	Ethanolic extract of E.S. Leaves	Ethanolic section of E.S. Flowers
Carbohydrates	+	+	+
Tannins	-	+	+
Alkaloids	+	+	+
Glycosides	+	-	-
Flavonoids	+	+	-
Steroids	-	-	-
Proteins and Amino acids	+	-	+

(+) = Present, (–) = Absent

Table 3: Antioxidant Activity by DPPH Method

Concentration (μg/ml)	% Inhibition			
	Roots extract	Flower extract	Leaves extract	Ascorbic acid
100	22.3±1.64	11.66±1.63	14.15±2.31	39.32±1.62
200	46.9±2.35	26.52±1.25	26.34±1.64	51.64±1.52
300	66.8±1072	37.48±1.22	35.21±1.37	69.54±1.66
400	72.68±1.34	44.87±1.74	47.38±1.57	79.98±1.35
500	77.89±1.68	59.81±1.62	62.14±1.38	86.75± 1.65

Table 4: Change in Body Weight

Groups	Treatment	Body weight (gm)		% Change in B.W.
		Initial	Day 12	
I	Vehicle	156.54±3.68	157.21±2.98	-
II	Gentamicin	168.75±3.54	162.42±4.32	4.63
III	REES + GTN	158.62±4.06	154.35±3.68	2.87
IV	FEES + GTN	194.30±5.34	188.36±2.78	4.26
V	LEES + GTN	164.57±3.46	157.52±2.87	3.64

Where
G.T.N. - Gentamicin
REES – Root extract of *Elephantopus scaber*
FEES - Flower extract of *Elephantopus scaber*
LEES - Leaves extract of *Elephantopus scaber*

Table 5: Urine Analysis

Groups	Treatment	Volume of urine
I	Vehicle	2.65±1.67
II	Gentamicin	1.89±1.25
III	REES + GTN	3.34±2.35b**
IV	FEES + GTN	2.72±1.64
V	LEES + GTN	2.85±1.63

All values are mean ± SEM, n = 6. ** p<0.01

Table 6: Urine Analysis for Kidney Function Test

Groups	Treatment	Creatinine mg/day/ml	Urea mg/day/ml	Uric acid mg/day/ml
I	Vehicle	1.26±0.0034	2.37±0.0021	34.86±0.064
II	Gentamicin	4.13±0.0061a***	5.86±0.0035a***	53.64±0.084a***
III	REES + GTN	2.64±0.0082a*,b*	3.59±0.0046b**	46.57±0.064a**,b**
IV	FEES + GTN	3.53±0.0052a**	4.16±0.0027a**	49.76±0.034a***,b*
V	LEES + GTN	3.86±0.0067a**	4.65±0.0068a**	52.35±0.068a***

All values are mean ± SEM, n = 6. *p<0.05, ** p<0.01
a- Significance difference as compared to group-I (Vehicle)
b- Significance difference as compared to group-II (G.T.N.)

Table 7: Serum Analysis for Kidney Function Test

Groups	Treatment	Creatinine mg/day/ml	Urea mg/day/ml	Uric acid mg/day/ml
I	Vehicle	0.67±0.035	16.84±1.63	4.26±0.17
II	Gentamicin	0.93±0.085a***	23.54±1.34a***	8.68±0.76a***
III	REES + GTN	0.72±0.067a*,b**	19.73±1.65a*,b*	5.34±0.54
IV	FEES + GTN	0.86±0.036a**	22.06±1.67a***	7.26±0.59a***
V	LEES + GTN	0.88±0.058a***	22.84±2.63a***	7.67±0.34a***

All values are mean ± SEM, n = 6. *p<0.05, ** p<0.01
a- Significance difference as compared to group-I (Vehicle)
b- Significance difference as compared to group-II (G.T.N.)

Table 8: Histopathological Analysis

Groups	Treatment	Vacuolization in proximal tubular epithelial cells	Tubular Necrosis in proximal tubular epithelial cells
I	Vehicle	—	—
II	Gentamicin	+++	+++
III	REES + G.T.N.	+++	++
IV	FEES + G.T.N.	++	++
V	LEES + G.T.N.	+	+

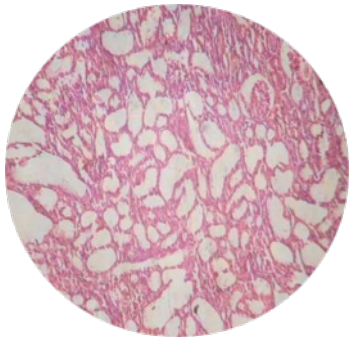

Figure 1: Histopathological Slide of Group I (Vehicle Group)

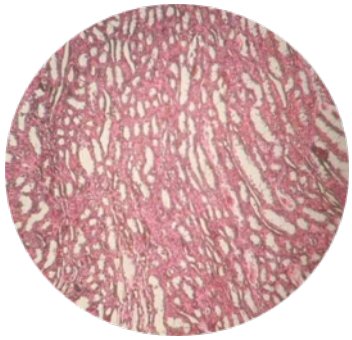

Figure 2: Histopathological Slide of Group II (Gentamicin Treated Group)

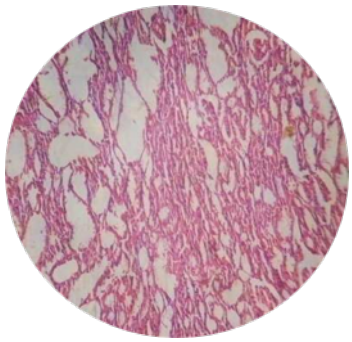

Figure 3: Histopathological Slide of Group III (RENN + G.T.N. Treated Group)

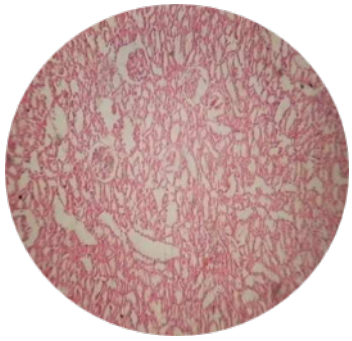

Figure 4: Histopathological Slide of Group IV (FENN + G.T.N. Treated Group)

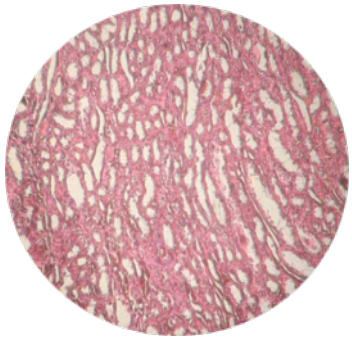

Figure 5: Histopathological Slide of Group V (LENN + G.T.N. Treated Group)

Physicochemical Analysis of Powder of *Elephantopus scaber* Leaves, Flowers & Roots

Standard published techniques were used to perform a physicochemical examination of the powdered leaves, flowers, and sources of the *Elephantopus scaber*. Table 1 presents the findings of the Physicochemical analysis.

Phytochemical Screening of *Elephantopus scaber* Roots, Leaves & Flowers

Elephantopus scaber roots, leaves, and flowers ethanolic section underwent phytochemical screening, which identified a variety of phytoconstituents including flavonoids, glycosides, alkaloids, and carbohydrates. Table 2 presents the findings of phytochemical analysis of an ethanolic extract of *Elephantopus scaber* roots, leaves, and flowers.

In vitro Antioxidant Activity of Ethanolic Extract of *Elephantopus scaber* Leaves Flowers & Roots

DPPH Method

Elephantopus scaber roots, leaves, and flowers ethanolic extract underwent phytochemical screening, which identified a variety of phytoconstituents, including flavonoids, glycosides, alkaloids, and carbohydrates. The phytochemical analysis of*Elephantopus scaber* ethanolic extract Flavonoids, glycosides, alkaloids, and carbohydrates were detected in the phytochemical screening of the ethanolic extract of the roots, leaves, and flowers of the plant. The results of a phytochemical examination of an ethanolic extract of the sources, leaves, and flowers of the *Elephantopus scaber* are shown in Table 3.

Effect of Ethanolic Extract of *Elephantopus scaber* Leaves Flowers & Roots on Body Weight and Urinary Volume

Compared to the control group, body weight significantly varies among the various treated groups. On repeated intraperitoneal injections of gentamicin, the body weight of the mice in the control group

decreased dramatically (Table 4 and Table 5).

Effect of Ethanolic Extract of *Elephantopus scaber* leaves Flowers & Roots on Urine and Serum Biochemical Analysis for Kidney Function Test

The effectiveness of the above *scaber* extract against gentamicin-induced kidney damage was assessed. On the 12th day of the experiment, Group iii showed significant reductions in urine but glomerular filtration rate, sulfur, and uric acid levels, although in comparison with the whole G.T.M. group. Besides this, on day 12, group iv has no noticeable change. Still, instead group v's urine or serum concentrations of creatinine, urea, and uric acid compared with the whole G.T.M. group (Table 6 and Table 7).

Effect of Ethanolic Extract of *Elephantopus scaber* Leaves Flowers & Roots on Histopathological Analysis

Animals in Group I (vehicle treatment) displayed typical proximal tubular and glomerular histopathology (Figure 1). The kidney histology of animals in group II (Gentamicin) demonstrated severe glomerular congestion, tubular necrosis, blood clot congestion, and the inclusion of inflammatory cells (Figure 2). Gentamicin was the only medication utilized during the treatment, and it only resulted in substantial vacuolization and necrosis (+++) in proximal tubular epithelial cells. Compared to the control group, animals in Group III (REES+GTN treated group) displayed less vacuolization and necrosis in proximal tubular epithelial cells (Figure 3). In comparison to Group iii (REES+GTN treated Group) and indeed the controlled study, there would be much lower vacuolization but instead fibrous necrosis throughout groups iv (FEES + G.T.N. treated Group) as well as v (LEES + G.T.N. allowed to treat Group) (Figure 4 and Figure 5). Compared to the Group treated with Elephantopus scaber root extract, the gentamicin group had considerably more significant rates of renal tissue necrosis (Table 8). The histopathology findings further supported the Elephantopus scaber root extract's ability to protect against gentamicin-induced Nephrotoxicity.

CONCLUSION

In summary, the current study shows that gentamicin causes an increase in renal tissue damage as well as nephrotoxicity indices, including creatinine, urea, and uric acid concentrations in the urine and serum. *Elephantopus scaber* root extract can protect the kidneys from gentamicin-induced nephrotoxicity while improving kidney function. It is encouraged to do additional research with various phytoconstituents of such a retrieve to see a probable molecular mechanism of activity through gentamicin-induced nephrotoxicity.

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Conflict of Interest

The authors declare that there is no conflict of interest in this study.

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