Original Article

Protective Effect of Tinospora Bakis (Miers) Methanolic Extract on Gentamicin-Induced Nephrotoxicity in Rats

Nephroprotective Effects Methanol Extract Against Gentamicin-Induced Kidney Damage

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ABSTRACT

Objective: To investigate the potential nephroprotective effects of (Tinospora Bakis) methanol extract against gentamicin-induced kidney damage in rats.
Study Design: Experimental study
Place and Duration of Study: This study was conducted at the Central Veterinary Research Laboratory, Khartoum, Sudan from 1st February 2022 to 31st January 2023.
Methods: Wister albino rats were used as control groups (gentamicin only) and treatment groups (gentamicin + Tinospora Bakis extract at different doses). Induction of nephrotoxicity in rats using gentamicin. Administration of Tinospora Bakis methanol extract at different doses. Measurement of serum urea, creatinine, total proteins, and electrolytes. Histopathological analysis of kidney tissues.
Results: Gentamicin increased serum markers of kidney damage (urea, creatinine, total proteins).
Tinospora Bakis extract reduced these markers, indicating a protective effect. Gentamicin decreased serum electrolytes (sodium, potassium), which were restored by Tinospora Bakis extract. Histopathological analysis Tinospora Bakis extract prevented Gentamicin-induced nephrotoxicity, supported the protective effect of the extract.
Conclusion: Tinospora Bakis methanol extract exhibits nephroprotective activity against gentamicin-induced kidney damage, possibly due to the presence of bioactive compounds. Further research is needed to identify and characterize these compounds.
Key Words: Tinospora Bakis, nephrotoxicity, Gentamicin, urea, creatinine.

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INTRODUCTION

The kidneys concentrate and remove drugs, making them sensitive to drug-induced toxicity. Acute kidney injury (AKI) and chronic renal diseases are caused by drug-induced nephrotoxicity, according to several studies[1]. Drug-induced acute kidney injury (AKI) accounts for 20%-40% of cases, with aminoglycosides and beta-lactams being the most common culprits. Amphotericin B, acyclovir, tenofovir, and indinavir can also affect the kidneys in several ways.[2,3]

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Aminoglycoside antimicrobials were first isolated from actinomycetes Streptomyces griseus in 1940s and used for the treatment of tuberculosis. Members of aminoglycosides antibiotics have been discovered from several groups of Streptomyces including Gentamicin antibiotics from Micromonospora group[4].

Gentamicin has been widely used in experimental animal models of nephrotoxicity. The WHO estimates that 75%–80% of the world's population, mainly in developing nations, uses traditional medicine[5]. For thousands of years, Chinese herbal medicine has prevented and treated many diseases and is a popular supplemental therapy globally. Chinese herbal medicine has been associated to nephrotoxicity in recent decades, especially aristolochic acids, alkaloids, anthraquinones, flavonoids, and glycosides[6].

Twenty years ago, the African Summit of Heads of State and Government approved an action plan to evaluate traditional malaria, sickle-cell anemia, and hypertension treatments for safety, efficacy, and quality. Sudan has various herbal medicinal herbs whose activity and toxicity were studied[7]. Tinospora Bakis, a succulent woody climber in the Menispermaceae family, grows in tropical Africa and

Asia. Africans treat dyspepsia, flatulence, diarrhea, and rheumatism with the plant. A Burkina Faso study found that a combination of Tinospora Bakis, Swartzia madagascariensis, and Combretum glutinosum extracts effectively inhibited the chloroquine-resistant strain W2 of Plasmodium falciparum at 5 µg/ml (IC50 < 50 µg/ml).

Sudan conducted several investigations on Tinospora Bakis' therapeutic and harmful qualities. Tinospora Bakis aqueous extract was not hazardous to male Wistar albino rats at low doses, but 2000 mg/kg produced nephrotoxicity, according to Farah[8,1.] tested methanolic Tinospora Bakis extracts at various doses with Cymelarsan (arsenical substance) against Trypanosoma evansi infection in rats. Cymelarsan cleared T. evansi immediately at 0.25mg/kg body weight, while the extract cleared 50% with relapse two weeks later. The diterpenoid furanolactone from Tinospora Bakis reduced inflammation in rats at 700mg/kg BW, outperforming Aspirin[9]. Tinospora Bakis has medicinal potential, therefore this study studied methanol extract's nephroprotective effects against Gentamicin-induced kidney injury in Wister albino rats.

METHODS

Preparation of plant extract: Tinospora Bakis leaves and branches were cleared of dust and soil with distilled water, cut into small pieces, and dried at room temperature for two weeks. Blended dried substance made fine powder. 500 gm of powder was steeped in 1 L of 80% methanol for 4 hours and filtered with Whatmann No. 1 filter paper. The filtration was vacuum-evaporated and stored. The extract weight for each group was estimated based on animal body weight and dissolved in distilled water.

Phytochemical analysis: Tinospora Bakis methanolic extract was phytochemically analyzed using [10] and [11] methods. Qualitative and quantitative analysis were necessary to identify plant extracted bioactive components used in medication manufacturing and separate its ingredients.

Braymer test (tannin test): Mix 1 ml of plant filtrate with 3 ml distilled water. Three drops of 10% ferric chloride were applied. A blue-green hue indicates a happy outcome[12].

The phenolic compound's iodine test used a few drops of iodine solution in 1 ml of plant filtrate. Tangible color indicates success.

Test for flavonoids: ammonia test: Volume of 1 ml of plant filtrate was diluted with 5 ml of ammonia solution. With caution, the concentrated sulfuric acid was applied. A positive outcome is denoted by the yellow hue that was acquired[12].

Test for alkaloids: (Dragen Droff's test): A small volume of plant filtrate was mixed with 2 ml of Dragen Droff's reagent. A reddish-brown precipitate indicated a successful outcome[13,14].

Test for glycosides: Keller-Killani test: In the Keller-Killani test, 1 ml of aqueous plant filtrate was mixed with 1.5 ml of glacial acid. A few droplets of a ferric chloride solution containing 5% were then added. Positive outcomes are denoted by the color green[15,14].

Saponins Test: 1 ml of plant filtrate was combined with 9ml of distilled water and agitated to determine Saponin. A positive outcome is denoted by the formation of bubbles[15].

Experimental Animals: The Khartoum Atomic Energy Research Institute donated 40 100-150-gram Wister albino rats of both sexes. The rats were housed in cages with access to water, a rat formula food (corn, powder, and protein), and standard ambient conditions at 22-±2°C Ten days were allowed for acclimatization before trials. An international protocol was followed for this lab animal investigation. Laboratory animal care principles (NIH Publication No. 85-23, modified 1985) and Sudan's Ministry of Cabinet Veterinary Council ethical approval.

Experimental design: Forty male and female rats were placed into four 10-rat groups. TBE was given orally via nasogastric tube. Group A (healthy control): 12 days of normal feeds, water and food. Group B (control): Injected with 80 mg/Kg BW Gentamicin IP daily from day 0 to day 6. Group C (TBE 300): Injected 80 mg/Kg BW Gentamicin IP daily from day 0 to day 6. Oral TBE at 300mg/Kg BW was given from day 0 to day 12. Group D (TBE 600): Injected 80 mg/Kg BW Gentamicin IP daily from day 0 to day 6. TBE was given orally at 600mg/Kg BW from day 0 to 12.

Biochemical analysis: Blood was taken from the ocular vein under anesthesia into sterile plain vacutainer tubes on days 0, 6, and 12 and kept overnight at 4^0C. Serum was centrifuged at 13000 rpm for 5 min at 4^0C and kept at -20^0C. Following the machine instructions, Sysmex Haematology System KN-21N (Germany) was used to measure urea, creatinine, and potassium in serum. After the experiment, rats were slaughtered, and their kidneys were cleansed in normal saline. For histological examination, each rat's right kidney was removed and placed in 10% formalin. The left kidneys were fixed in 10% formalin.

Histological methods:

Tissue Preparation: Rats were euthanized under anesthesia. Then after this kidneys removed quickly and carefully. Then thoroughly dissected the kidneys for cortex and medulla tissues. These tissue samples were treated in 10% neutral buffered formalin to preserve cellular structure at room temperature for 24 hours.

Tissue Processing: Alcohol concentrations in 60%, 70%, 85%, 90%, and 99% dehydrated fixed kidney tissue samples. Using a microtome, we embedded them in paraffin wax. Following the process, tissues were

sectioned into 4-5 µm slices using a microtome. These slices were placed on glass slides, dried, and stored at room temperature until analysis.

Hematoxylin and Eosin (H&E) Staining:

Representative slices from each experimental group were Hematoxylin and Eosin stained to assess tissue shape and structural integrity. After removing the wax, the tissue sections were rehydrated with alcohol solutions and stained with hematoxylin eosin according to the manufacturer's instructions. The sections were immersed in the solution for 5 minutes, rinsed with running water, then counterstained with eosin for 2 minutes. After that, alcohol dehydrated the parts. Cleared with xylene before mounting.

Statistical Analysis: Data obtained from both biochemical assessments were subjected to statistical analysis using two-way Anova (ANOVA) to determine the significance of the observed changes between experimental groups. Results were expressed as mean ± standard deviation, and p-values less than 0.05 and 0.01 were considered statistically significant.

RESULTS

Effects of Tinospora Bakis methanolic extract on serum creatinine: On day 6, group B (control) without TBE after Gentamicin injections had a considerably higher creatinine level (Table 1). On day 12, group C received a modest dose of 300mg/Kg (TBE 300) of Gentamicin, which significantly reduced creatinine levels ($P < 0.05$) compared to group B (Table 1). In group D, raising the dose of the extract (TBE 600) to 600 gm/Kg significantly ($P < 0.05$) reduced creatinine levels produced by Gentamicin. TBE increased creatinine levels after Gentamicin injection at both concentrations, but it did not return them to the baseline level of healthy control group A (Table 1).

Effects of Tinospora Bakis methanolic extract on serum urea: Gentamicin injection significantly raised urea levels at day 6 and 12 ($P < 0.05$) in group B. Low dose (TBE 300) reduced urea in group C but not much compared to B. The high dose of (TBE 600) in group D significantly reduced urea levels ($P < 0.05$) compared to control group B. The healthy control group A's urea levels increased somewhat at days 6 and 12.

Effects of Tinospora Bakis methanolic extract on serum total proteins: Gentamicin administration resulted in a significant ($P < 0.05$) increase in total protein at day 12 for control group B compared to healthy control group A (Table 3 Group C received TBE 300 to restore total protein to healthy control group A levels. In addition, TBE 600 treatment led to a substantial decrease ($P < 0.05$) in total protein levels compared to healthy group A on day 0 (Table 3). Alkaloids may explain Tinospora Bakis' nephroprotective properties.

Effects of Tinospora Bakis methanolic extract on serum Sodium: Gentamicin injection significantly reduced salt levels ($P<0.05$) in group B compared to healthy control group A. Low-dose treatment of the extract (TBE 300) significantly raised salt levels ($P < 0.05$) on day 12 (Table 2). Sodium levels in the serum considerably rose ($P<0.05$) and returned to healthy group A values at days 6 and 12 (Table 2).

Effects of Tinospora Bakis methanolic extract on serum Potassium: Serum potassium levels considerably decreased ($P<0.05$) in group B after Gentamicin injections (Table 2). The low dose of the extract (TBE 300) raised potassium levels at day 6 and 12 to those of the healthy control group A. High-dose TBE 600 administrations led to significant ($P<0.05$) potassium increases in serum at both time-points, comparable to healthy control group A (table 2).

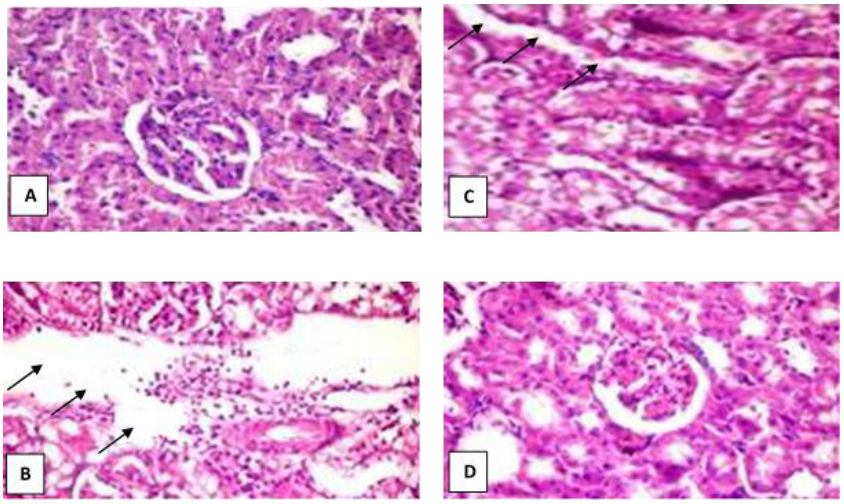

Figure 1: H&E-stained rat kidney tissue treated with Tinospora Bakis methanolic extract. A) Healthy controls have intact tubules and glomeruli. Gentamicin-treated groups have nephrotoxicity. (C) Histological structure changes somewhat in the 300 mg/kg BW TBE/Gentamicin group. (D) Tinospora Bakis extract at 600 mg/kg BW prevented Gentamicin-induced nephrotoxicity. Magnification: 400x.

Table No.1: **Effects of Tinospora Bakis methanolic extract on serum urea and creatinine**

Groups	Urea			Creatinine		
	Day 0	Day 6	Day12	Day 0	Day 6	Day 12
A	32.24± 0.61	38.18±0.68	42.20±1.82	0.28±0.02	0.31±0.03	0.320.04±
B	35.82± 0.84	45.42*± 1.22	58.24*±2.12	0.34±0.02	2.50*±0.08	4.12*±0.06
C	38.40±0.92	42.21± 2.10	51.41*±4.21	0.36± 0.02	0.98± 0.28	1.64*±0.28
D	40.82±1. 21	41.4± 0.6	45.6*±0.8	0.38±0.04	0.28± 0.06	0.91*± 0.04

Group A: Serves as control. Group B: Injected with Gentamicin IP daily at a dose of 80 mg/Kg BW
Group C: Gentamicin IP daily at a dose of 80 mg/Kg BW + (TBE 300).
Group D: Gentamicin IP daily at a dose of 80 mg/Kg BW + (TBE 600).
The difference was found to be significant (*P<0.05, when compared with group B (control).

Table No. 2: Effects of Tinospora Bakis methanolic extract on serum sodium and potassium

Groups	Sodium (Na+)			Potassium (K+)		
	Day0	Day6	Day12	Day0	Day6	Day12
A	152.2±4.32	153.12±4.81	157.3±3.62	5.21±0.24	5.18±0.34	5.46±0.38
B	157.21±4.28	146.32*±3.42	132.48*±2.82	5.24±0.26	4.69±0.21	3.384*±0.19
C	156.38±4.21	151.38±2.12	148.23*±2.24	5.12±0.26	5.41±0.31	5.21*±0.21
D	157.24±3.84	156.42*±2.46	158.21*±1.84	5.18±0.08	5.52**±0.21	5.88±0.28

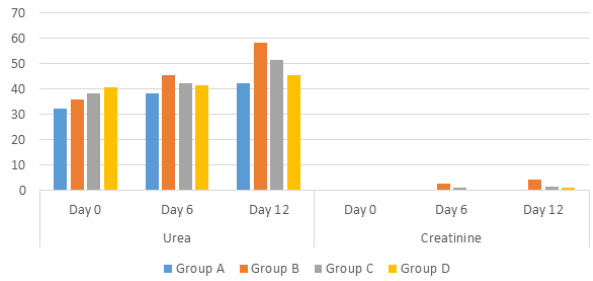

Figure No.1: Effects of Tinospora Bakis methanoloic extract on serum urea and creatinine

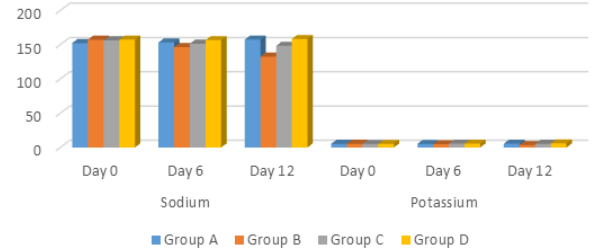

Figure No.3: Effects of Tinospora Bakis methanoloic extract on serum sodium and potassium

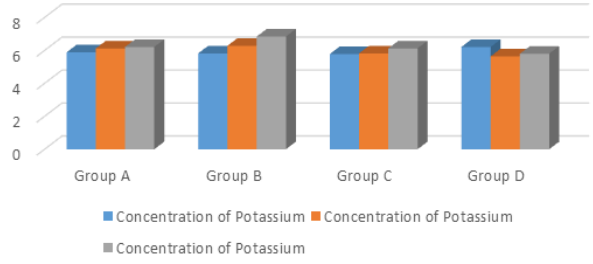

Figure No.4: Effects of Tinospora Bakis methanoloic extract on serum total proteins

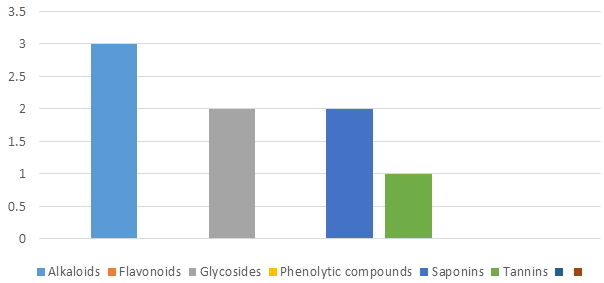

Figure No.5: Results of Phytochemical Analysis for Tinospora bakis Extract

Effects of Tinospora Bakis methanolic extract on renal histology: A healthy control had normal tubules and glomeruli. Gentamicin (80 mg/Kg BW) daily from day 0 to day 6 produced tubular dilatation, cast formation, and cellular integrity loss in group (B Tinospora Bakis extract 300 mg/kg BW (TBE 300) with Gentamicin produced tubular dilatation, cast formation, and cellular collapse in group (C), similarly in group B. Like group (A) and a control group, group (D) treated with Tinospora Bakis extract (TBE) 600mg/kg BW and Gentamicin at 80 mg/kg BW demonstrated protection against Gentamicin-induced nephrotoxicity, with normal tubule histology and superior structural integrity.

Table No.3: Effects of Tinospora Bakis methanolic extract on serum total proteins

Group	Total Protein		
	Day 0	Day6	Day12
A	5.88±0.18	6.12±0.42	6.21±0.38
B	5.82±0.22	6.28±0.40	6.84*±0.38
C	5.78±0.21	5.82±0.61	6.12±0.64
D	6.21±0.40	5.640.38	5.80*±0.52

Table No.4: Phytochemical results:

Test	Result
Alkaloids	+ + +
Flavonoids	
Glycosides	+ +
Phenolytic compounds	_
Saponins	+ +
Tannins	+

DISCUSSION

Nephrotoxicity occurs with aminoglycoside medicines notwithstanding their advantages. Nephrotoxicity is caused by toxins. Gentamicin's therapeutic application is limited by this considerable effect[16]. Medicines, chemicals, and environmental pollutants can affect the kidneys, which are vascular and filter, reabsorb, and secrete[17]. The methanolic Tinospora Bakis extract did not kill or affect animals, who survived the experiment. These findings are congruent with[8], which revealed that aqueous extract from Tinospora Bakis from the same region in Sudan and the same strain of rats does not harm hematological, biochemical, or renal histology at 500 mg/kg body weight. Tinospora Bakis aqueous extracts at 2000 mg/kg BW were safe in Wistar rats[18].

Nephrotoxicity occurred in the control group after 6 days of Gentamicin administration. Increased creatinine, urea, total proteins, and reduced sodium and potassium (Tables 1–2). Gentamicin injection increased urea and creatinine in rats[19,20,21]. Renal toxicity raises blood creatinine and urea, indicating renal impairment[22]. Concentrations of total protein, salt, and potassium also indicated renal damage[23].

Tinospora Bakis' nephroprotective properties were examined by oral gavage of its methanolic extract at low dose (300 mg/kg/BW) to group C and high dose (600 mg/kg/BW) to group D daily. Rats with modest extract doses had lower urea and creatinine than with Gentamicin. At 600 mg/kg/BW, the plant extract lowered serum urea, creatinine, and total proteins, proving its nephroprotective characteristics. This study's high dose was safe and nonfatal[8,18]. Petroslinum crispum leaves methanolic extract protected rats from Rifampin in another investigation[4]. The plant extracts elevated urea and creatinine. This study detected nephrotoxicity by measuring serum sodium and potassium imbalance. Tinospora Bakis methanolic extract protection. Gentamicin injections lowered sodium and potassium, but plant extract raised them. Table-2 demonstrates larger plant extract doses boosted it.

Renal damage was evident in the control group's tubular dilatation, cast formation, and cellular integrity loss (Fig.1). Aminoglycoside produced proximal and distal tubule cytotoxicity, acute interstitial nephritis, electrolyte-wasting tubulopathy, and Fanconi-like syndrome[3]. Kang[22] said Gentamicin-induced nephrotoxicity affects mesangial and renal proximal tubule cells. Renal tissue cellular and structural integrity alterations often accompany nephrotoxicity. Gentamicin injections for 6 days in control group B rats produced nephrotoxicity.

Tinospora Bakis (TBE) methanolic extract decreased tubular dilatation and glomeruli effects of Gentamicin-induced histological damage in the low-dose (300 mg/kg/BW) group (C). Group D had no histological abnormalities, demonstrating that Tinospora Bakis (TBE) methanolic extract prevents Gentamicin-induced nephrotoxicity. We found alkaloids, saponins, tannins, and glucosides. Gentamicin preserves rats' kidneys because bioactive chemicals occur naturally. High alkaloids and Saponin levels made Tinospora Bakis (Table 3) the most nephroprotective. High alkaloids and saponin concentration in Tinospora Bakis may treat renal toxicity.

CONCLUSION

This study showed that Tinospora Bakis methanolic extracts were safe for rats. High-dose Gentamicin-induced nephrotoxicity was prevented by oral plant extract gavage. The plant extract's bioactive component can be isolated and purified to determine an anti-nephrotoxic compound.

Data Availability: The data used to support this study are included in the paper. However, data are available from the corresponding author upon responsible request.

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Author's Contribution:

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Drafting or Revising Critically:	Nada Mohamed Suliman, Anil Bangalore Shivappa, Ahmed Hashim and Sanusi Mohammad Bello
Final Approval of version:	All the above authors
Agreement to accountable for all aspects of work:	All the above authors

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