

Phytochemical Screening and Evaluation of Ameliorating Effect of *Aleuritopteris bicolor* (Roxb.) Fraser-Jenk Leaves Extract on Renal and Hepatic Impairment in a Rat Model of Gentamicin-Induced Renal Toxicity

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ABSTRACT

Background: The fern species *Aleuritopteris bicolor* (AB), in the Pteridaceae family, traditionally used for wound healing and treating various ailments.

Aim: This study was conducted to evaluate *Aleuritopteris bicolor* (AB) hydro ethanol leaf extract potential in mitigating gentamicin-induced nephrotoxicity and hepatotoxicity in Albino rats.

Methods and Materials: This study was achieved by performing a phytochemical test on AB hydro ethanol leaves extract and administering hydro ethanol extract of AB leaves orally and gentamicin (80 mg/kg/day) intraperitoneal for a period of seven consecutive days to male albino rats, followed by analysis of biochemical function, histopathology, and the weight of the kidney and liver after the eighth day. SPSS version 23 was used for data analysis. Results were presented as mean $\pm$ standard deviation (n=6). Statistical analysis involved one-way ANOVA followed by post hoc least significant difference (LSD) test.

Results: From the phytochemical screening, *Aleuritopteris bicolor* (AB) hydro ethanol extract was found to contain flavonoids, phenols, saponins, and tannins. Acute toxicity testing showed its safety up to 5000 mg/kg. Gentamicin administration (Group II) resulted in a significant ($p < 0.001$) increase in urea (154.07 ± 6.22 mg/dl), creatinine (8.90 ± 0.51 mg/dl), and uric acid (3.27 ± 0.74 mg/dl), indicating renal dysfunction compared to the negative control group (distilled water). Co-treatment with ascorbic acid (Group III) and varying doses of *Aleuritopteris bicolor* (AB) extract (Groups IV, V, and VI) led to significant reductions in urea and creatinine levels, with the 500 mg/kg AB extract dose showing the most notable effects ($p < 0.001$) compared to the gentamicin-only group. Histopathological analysis revealed that gentamicin caused tubular degeneration, colloid cast formation, and glomerular injury, while treatment with AB extract minimized these damages. Additionally, gentamicin caused significant increases in serum ALP ($p < 0.001$), AST ($p < 0.001$), and ALT ($p < 0.001$) compared to the control group. Treatment with AB extract significantly reduced these enzymes ($p < 0.001$) compared to the gentamicin-only group. Histological analysis showed the gentamicin group had portal inflammation and hepatocyte degeneration, while AB extract minimized these changes, supporting its protective effects against renal and hepatic toxicity.

Conclusions: These findings suggest that *Aleuritopteris bicolor* extract effectively mitigates gentamicin –induced nephrotoxicity and hepatotoxicity in Albino rats, demonstrating potential for therapeutic use.

Keywords: *Aleuritopteris bicolor*, phytochemical analysis, renal protective effects, hepatoprotective effects, gentamicin toxicity.

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INTRODUCTION

Nephrotoxicity refers to kidney damage caused by drugs and chemicals and is a significant contributor to chronic kidney disease, affecting more than 27 million individuals (1). It often arises as a result of acute kidney injury, with chemical-induced nephrotoxicity accounting for approximately 20% of these cases (2). Prolonged use of the antibiotic such as gentamicin can lead to kidney damage by generating oxidative stress within the kidney cells. This damage impairs the functioning of proteins, lipids, and DNA, triggering inflammation and disrupting the transport of sodium, which ultimately causes cellular swelling and death (3). Similarly, gentamicin alters various body chemicals such as liver enzymes, creatinine, electrolytes, uric acid, urea, protein, and inflammatory substances. Kidney injuries can also impact other organs, including the liver. Renal ischemia-reperfusion injury can occur, leading to liver damage characterized by leukocyte infiltration, congestion, and cellular necrosis. Hepatotoxicity, caused by drugs, is a major global healthcare concern, responsible for 75% of fatal adverse drug reactions and 5% of hospitalizations.(4)

Certain fern species such as *Adiantum capillus*, *Dryopteris filix-mas*, *Polypodium leucotomos* are documented to possess hepatoprotective while *Adiantum capillus* is also recognized for its nephroprotective effects against the toxic impacts of chemicals (6,7). Among various fern species, *Aleuritopteris bicolor* (AB) (Roxb.) Fraser-Jenk is traditionally used for improving kidney function in animals as well as treating gastrointestinal diseases in human within the local community of Lekhnath Pokhara and by specific ethnic groups in Nepal(8). However, there exists a scientific gap in understanding the therapeutic potency of *Aleuritopteris bicolor* (AB) for kidney function. To address this gap, further research is essential to explore the potential therapeutic benefit of *Aleuritopteris bicolor* (AB) on kidney and liver functions.

METHODS AND MATERIAL:

Plant Materials Collection

The leaves of *Aleuritopteris bicolor* AB hydroethanol

extract were dried in the shade after being collected from a field in Kaski, Lekhnath, Pokhara, Nepal. It was identified by Mr. Dhan Raj Kandel, Scientific Officer, the National Herbarium and Plant Laboratory, Godavari, Lalitpur, Nepal. A voucher specimen (no. PUH-2022-39) was stored in the herbarium section of School of Health and Allied Sciences, Pokhara University, Nepal. Samples of plant leaves were ground up and used for extraction.

Preparation of Extract of Plant Species

Using the method of cold maceration with 70% ethanol in a ratio of 1: 10 (powdered crude drug: solvent = 100 gm : 1000 ml), leaf powder was macerated for three days in a row in a dark area. The resulting extract was then filtered through Whatman filter paper. The obtained filtrates were concentrated in a rotary evaporator at 40°C, and the extracted product was stored in a vacuum desiccator until it was needed.(9)

Phytochemical Screening

According to established procedures, the obtained crude extract underwent a phytochemical analysis to identify the presence of alkaloids, flavonoids, phenols, terpenoids, tannins, glycosides, and reducing sugar. Any appearance of color, change in color, or precipitate formation was used as a sign that these tests had been successful(10).

Studies animals

Fifty-four male albino rats (200–270 g) were obtained from the animal house department of plant resources, Kathmandu, Nepal. They were housed in normal cages at room temperature (25 ± 3 °C, $55 \pm 5\%$ humidity, 12 h natural light-dark cycle) at the primate facility of the University of Pokhara, Nepal to acclimate with standard pellets and water and were housed for a week. All tests and procedures were performed in accordance with Organization for Economic Co-operation and Development (OECD) guidelines and approved by the Ethics Committee of the Institutional Review Committee (IRC), Pokhara University Research Center with reference number (02/079/080).

Acute toxicity studies

An acute oral toxicity study, structured according to the fixed dose procedure following OECD 420 guideline, aimed to systematically assess the acute toxicity of the AB extract in male albino rats(11). The study protocol included an overnight fasting period with water access for the rats. On the following day, three groups each consisting of five rats, received a single oral dose of the AB extract at 1000 mg/kg, 3000 mg/kg, and 5000 mg/kg in the morning. Following, individual rats were closely observed at 60, 120, and 240 minutes after administration to monitor immediate effects or signs of toxicity. Surviving rats were continuously monitored for 14 days to detect delayed signs or severity of observed toxicity and mortality(11).

In vivo experimental design

The improvement in liver and kidney function during acute renal toxicity by the test samples was investigated using a method previously described for gentamicin (GM)-induced nephrotoxicity .(12) Thirty six male albino rats (200–270 g) were weighed, divided into six groups (n = 6), and was acclimatized with sufficient fresh water and food for one week.

The animals included in the study were randomly assigned to six equal groups (n=6) as follows:

Group I: Control (distilled water, 1 ml /kg/day orally) for 7 days. Rats in this group received distilled water (1 ml/kg/day) orally for 7 days. This served as the baseline group with no exposure to gentamicin or test substances.

Group II: Gentamicin (80 mg/kg/day I.P) for 7 days. This group was designed to induce nephrotoxicity and serve as the toxic control.

Group III: Ascorbic acid (200 mg/kg/day orally) + Gentamicin (80mg/kg/day I.P.) for 7 days. This group aimed to test the protective effect of ascorbic acid against gentamicin-induced nephrotoxicity.

Group IV: Extract (125 mg/kg/day orally) + gentamicin (80mg/kg/day I.P.) for 7 days. This group aimed to assess the protective effects of the lower concentration of the extract.

Group V: Extract (250 mg/kg/day orally) + Gentamicin (80mg/kg/day I.P.) for 7 days. This group aimed to assess the protective effects of the moderate concentration of the extract.

Group VI: Extract (500 mg/kg/day orally) + Gentamicin (80mg/kg/day I.P.) for 7 days. This group aimed to assess the protective effects of the higher concentration of the extract.

Biochemical Estimation:

During the 7-day experimental period, daily administrations were conducted. Blood samples were collected with the help of heparin-coated capillaries from the retro-orbital sinus on day 8 under mild anesthesia using ether. The collected blood was allowed to coagulate, and serum was separated by centrifugation at 3000 rpm for 10 minutes. Serum samples were then analyzed for kidney function markers including urea, creatinine, and uric acid, as well as liver enzymes (ALT, AST, and ALP) to assess the impact of gentamicin toxicity and the protective effect of the test substances. A diagnostic kit from thermo fisher scientific and sigma-aldrich was used for each assessment in accordance with the manufacturer's instructions (12).

Histopathological Examination:

Kidney and liver weights were measured at the end of the study by excising the organs post-mortem and expressing them as absolute weights. Both kidneys and liver were gathered, weighed, and preserved for at least 24 hours in 10% buffered formaldehyde. Similarly liver and kidney samples were dehydrated with ethanol (80%), cleared in xylene and was embedded in paraffin wax. Microtome was used to carve a section of tissue measuring 5 mm. Hematoxylin and eosin were used to stain the sections in order to detect histopathological alterations under a 10X microscope to evaluate morphological changes. (12) The results from all experimental groups were compared to the control and gentamicin-only groups to determine the level of protection offered by ascorbic acid and the plant extract against gentamicin-induced toxicity.

Statistical analysis

IBM Statistical Package for Social Sciences (SPSS) software version 23 was used for data analysis, and all data were expressed as mean $\pm$ standard deviation (n=6), and statistical analysis was conducted using one-way ANOVA followed by a post hoc LSD (Least significant difference) test. The significant effects are highlighted based on the provided p-values

RESULTS AND DISCUSSION PHYTOCHEMICAL TEST

The extracts from the plant species *Aleuritopteris bicolor*(AB) was subjected to various phytochemical tests and the tests revealed the presence of flavonoids, phenols, saponins, and tannins as indicated in **table 1**

Table 1. Qualitative phytochemical data of plant species extract

Phytochemical Constituent	Results of AB extract
Alkaloids	-
Flavonoids	+
Phenols	+
Glycosides	-
Saponins	+
Carbohydrates	-

Note: + present, - absent

The plant *Aleuritopteris bicolor* (AB) has been used as a traditional medicinal for treating different ailment such as wound healing, respiratory diseases, rheumatic conditions and digestive disorder.(13) In the present investigation, phytochemical screening of AB extract revealed the presence of flavonoids, phenols, saponins, and tannins, while alkaloids, glycosides, and carbohydrates were not detected in table 1. Flavonoids and phenols are known for their antioxidant properties and have been associated with various health benefits. They possess potential anti-inflammatory, anti-cancer, and neuroprotective, nephroprotective, hepatoprotective effects(14) · Studies on the hepatoprotective effects of flavonoids have shown their ability to mitigate liver damage and support liver function(15, 16). Furthermore saponins and tannins have been reported to possess anti-inflammatory, immunomodulatory and wound healing activities respectively(17) (18). This suggest that the presence of flavonoids, phenols, saponins and tannins in the AB extract might contribute to its tissue protective,

alleviate inflammatory conditions, regulate immune response and promote tissue repair through collagen formation. The presence of flavonoids and phenols in the AB extract suggests that it may have potential therapeutic properties.

Acute toxicity studies

No toxic effects or behavioral changes were observed in rats at fixed dose of 1000 mg/kg, 3000 mg/kg, and 5000 mg/kg during monitoring periods of 60, 120, and 240 minutes, as well as up to 14 days. Additionally, no mortality was observed at the highest administered dose of 5000mg/kg. This absence of mortality suggests that the LD₅₀ (lethal dose for 50% of the test animals) would exhibit toxicity or mortality, exceeds the highest tested dose of the extract 5000 mg/kg).In terms of acute toxicity, the absence of toxic effects and behavioural changes in rats at fixed doses of 1000 mg/kg, 3000mg/kg and 5000mg/kg, observed throughout the monitoring periods of periods of 60, 120, and 240 minutes, as well as up to 14 days, indicates a notable safety profile for the *Aleuritopteris*

bicolor (AB) extract in acute oral exposure. The consistent lack of adverse reactions suggests that the extract even at the highest tested dose of 5000mg/kg, doesn't elicit harmful physiological or behavioural responses in male albino rats. Furthermore, the absence of mortality at the highest administered dose reinforces the conclusion that the LD₅₀, representing the lethal dose for 50% of the test animals, surpasses the highest tested dose of the extract. This outcome indicates an absence of acute toxicity of the AB extract up to 5000mg/kg, when administered orally. Previous study conducted in acute toxicity of *Polypodium feei* root extract revealed no adverse effects in rats up to 5000mg/kg, supporting the present data of a low toxicity potential for fern species (19).

Effect of AB extract on serum creatinine, urea, and uric acid

As shown in the Table 2, administration of gentamicin

(Group II) led to a significant $p < 0.001$, increase in urea, and creatinine levels, indicating renal dysfunction. However, treatment with ascorbic acid in combination with gentamicin (Group III) resulted in increase in these biomarkers compared to the GM group. The groups treated with various doses of the extract alongside gentamicin (Groups IV, V, and VI) showed significant ($p < 0.001$), reductions in urea, and creatinine levels compared to the GM group, indicating potential properties of the extract. Notably, the highest dose of the extract (500mg/kg) demonstrated the most significant $p < 0.001$, decrease in creatinine levels. Similarly, gentamicin (Group II) led to a significant elevation in uric acid levels compared to the negative control (Group I), while co-treatment with ascorbic acid and various dose of plant extract didn't show any significant control in elevated uric acid level.

Table 2. Data representing level of serum creatinine, uric acid and urea in different groups of treatment

Experimental Group		Serum concentration (mg/dl) of		
		Uric acid	Urea	Creatinine
Group I	Negative Control (Distilled water)	2.86±0.73 ^{###}	46.36±2.3 ^{###}	1.75±0.40 ^{###}
Group II	Gentamicin	3.27 ±0.74	154.07± 6.22 ^{***}	8.90 ± 0.51 ^{***}
Group III	Ascorbic acid + Gentamicin	3.56±0.84	128.99 ±4.42 ^{***###}	6.82 ± 0.47 ^{***###}
Group IV	125mg/kg extract + Gentamicin	3.01±0.67	134.00 ± 7.18 ^{***###}	6.84 ± 0.10 ^{***###}
Group V	250mg/kg extract + Gentamicin	3.23 ± 0.72	117.04 ±3.82 ^{***###}	6.82 ± 0.49 ^{***###}
Group VI	500mg/kg extract + Gentamicin	2.83 ± 0.66	89.27 ± 7.27 ^{***###}	3.49±0.26 ^{***###}

Note: Data expressed as mean ± standard deviation (n=6). One –way ANOVA followed by a post hoc LSD test was used for comparison between different groups. * Significant change in comparison with the control group at $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$, # significant change in comparison with the GM group at $p < 0.05$, ^{##} $p < 0.01$, ^{###} $p < 0.001$.

Gentamicin is an antibiotic commonly used to treat various bacterial infections. The adverse effects associated with gentamicin use is nephrotoxicity, as refers to kidney damage,(20) which involves renal accumulation of the drug, generation of reactive oxygen species, mitochondrial dysfunction, apoptosis, inflammation and increased in creatinine, urea, uric acid etc.(21) Gentamicin can disrupt

the normal fluid balance within the kidney, leading to the accumulation of interstitial fluid. This fluid build-up can contribute to the increase in kidney weight.(22)In present study, effect of treatments on biochemical parameter, weight, histostructure of kidney and liver was assessed. Based on the data presented in Table 2, it can be concluded that administration of gentamicin (Group II) resulted in

renal dysfunction, as evidenced by significant increase in urea and creatinine levels. This aligns with previous finding that have consistently reported the nephrotoxic effects of gentamicin (23). However, treatment with ascorbic acid in combination with gentamicin (Group III) and various doses of the extract alongside gentamicin (Groups IV, V, and VI) showed renoprotective properties. In terms of urea and creatinine levels, Group III (ascorbic acid + gentamicin) exhibited increased compared to Group II (gentamicin only). This suggests that ascorbic acid may have a protective effect against gentamicin-induced renal dysfunction. This finding is consistent with studies that have explored the antioxidant properties of ascorbic acid and its ability to counteract oxidative stress- induced renal damage (24). Furthermore, Groups IV, V, and VI, which received different doses of the extract along with gentamicin, demonstrated significant reductions in urea and creatinine levels compared to Group II. These findings indicate the potential renoprotective properties of the extract, with the highest dose (500mg/kg) showing the most significant decreased in creatinine levels, Table 2. Comparing these findings with other research studies, our results aligns with results of other plant species like *Adiantum capillus* a fern extract demonstrated the renoprotective effects against cisplatin-induced

nephropathy(7). Similarly, the antioxidant and anti-inflammatory properties of various phytoconstituents have been documented in studies supporting the studies, that natural compounds may offer protection against drug-induced nephrotoxicity (25) (26) (27).

Effect of AB extract on kidney weight

The data presented in Table 3, represents the percentage weight of rat kidneys (right and left) in different treatment groups. As the results indicate that treatment with Gentamicin (Group II) led to a significant increase in the weight of both the right and left kidneys compared to the negative control group (Group I). Group III received Ascorbic acid along with Gentamicin, but no significant difference in kidney weight was observed compared to the Gentamicin group. Groups IV, V, and VI received different doses of an extract in combination with Gentamicin. Group IV (125mg/kg extract + Gentamicin) and) did not show a significant difference in kidney weight compared to the Gentamicin group. However, Group V (250mg/kg extract + Gentamicin) and Group VI (500mg/kg extract + Gentamicin) demonstrated a significant $p < 0.05$, $p < 0.01$ decreased in the weight of both kidneys respectively, compared to the Gentamicin group.

Table 3. Data representing the % weight of rat kidney (right and left) in different group of treatment

Experimental Group		Weight of Kidney (% Absolute value)	
		Right Kidney	Left Kidney
Group I	Negative Control (Distilled water)	0.33±0.055 ^{##}	0.31±0.04 ^{##}
Group II	Gentamicin	0.55±0.00 ^{**}	0.53±0.01 ^{**}
Group III	Ascorbic acid + Gentamicin	0.54±0.017 ^{**}	0.52±0.005 ^{**}
Group IV	125mg/kg extract + Gentamicin	0.52±0.005 ^{**}	0.5±0.01 ^{**}
Group V	250mg/kg extract + Gentamicin	0.5±0.02 ^{**#}	0.48±0.001 ^{***}
Group VI	500mg/kg extract + Gentamicin	0.41±0.05 ^{***#}	0.4±0.005 ^{***#}

Note: Data expressed as mean ± standard deviation (n=6). One –way ANOVA followed by a post hoc LSD test was used for comparison between different groups. * Significant change in comparison with the control group at $p < 0.05$, $^{**}p < 0.01$, $^{***}p < 0.001$, # significant change in comparison with the GM group at $^{#}p < 0.05$, $^{##}p < 0.01$, $^{###}p < 0.01$.

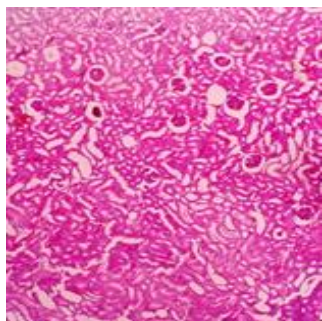
The percentage weight of the kidneys in different treatment groups also provides insights into the renal effects as shown in Table 3. Group II (gentamicin) showed a significant increase in the weight of both the right and left kidneys compared to the negative control group (Group I). This increased in kidney weight suggests kidney enlargement and possibly renal damage. This finding is consistent with previous studies that have reported an association between inncreased kidney weight and nephrotoxic effects of gentamicin (28) (29). Group III (ascorbic acid + gentamicin) did not show a significant difference in kidney weight compared to Group II, indicating that ascorbic acid may not have a significant impact on kidney size in the presence of gentamicin-induced damage. This contrasts with the study on ascorbic acid which reported a reduction in kidney weight following ascorbic acid administration in a model of renal injury (30). However, Groups V and VI, which received higher doses of the extract (250mg/kg and 500mg/kg, respectively) along with gentamicin, demonstrated significant decreases in the weight of both kidneys compared to Group II Table 3. This suggests that the extract may have a dose-dependent effect on reducing kidney size and potentially protecting against gentamicin-induced kidney enlargement. These finding align with studies, which demonstrated the ability of plant extracts to

attenuate kidney hypertrophy in experimental model (31).

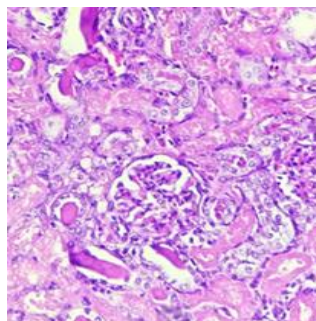
Effect of AB extract on kidney tissue

Histopathological examination of kidney sections

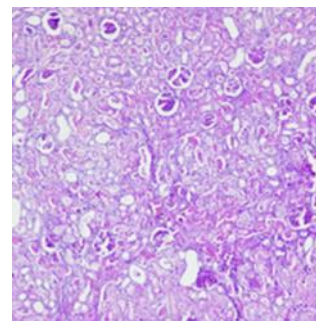
As shown in **Figure 1**, Group II (Gentamicin) shows degenerated tubules, colloid cast with chronic inflammatory cells in the interstitium, and acute glomerular injury. These findings indicate severe kidney damage and inflammation. Compare to this group, Group I and Group VI shows normal kidney parameters without any abnormalities. Group V shows mild glomerular injury, tubular cast, and mild chronic inflammatory cells in the interstitium, which was less severe than the findings in Group III. Additionally, in Group IV, tubular degeneration and chronic inflammatory cells was observed in the interstitium which was similar to Group III. However, there is no presence of glomerular injury in Group IV, distinguishing it from Group III, whereas Group Shows, focal fibrosis and mild chronic inflammatory cells in the interstitium. Compared to Group III, Group V shows some scarring and inflammation in the kidney, but without the acute glomerular injury seen in Group III. Group III displays chronic inflammation in the interstitium, along with degenerated tubules and colloid cast formation. The presence of ongoing inflammation and degenerative changes in the kidney suggests a similar severity of damage as seen in the Gentamicin group (Group II).



Negative Control(Distilled water)



Genta(80mg/kg)



Ascorbic acid (200 mg/kg) and
Genta (80 mg/kg)

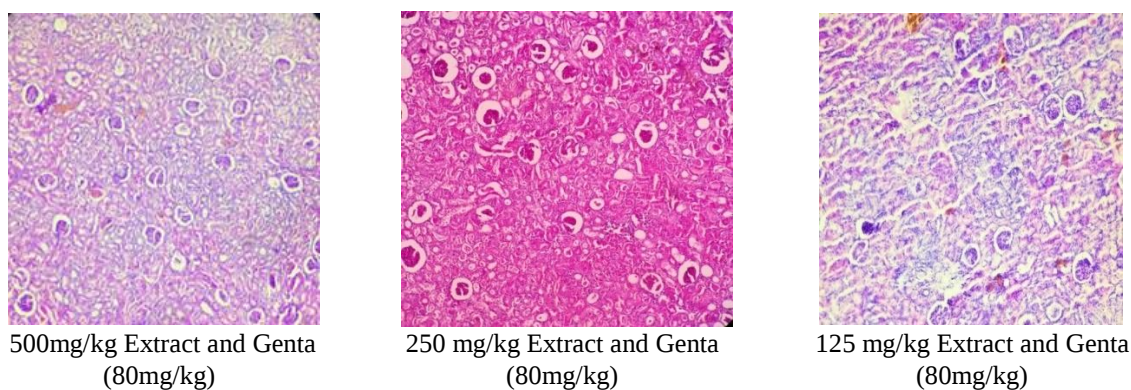


Figure 1. Effect of on kidney histomorphology in various groups

In **Figure 1**, the histopathological analysis of the kidneys further supports the findings. Group III (gentamicin) exhibited severe kidney damage and inflammation, including degenerated tubules, colloid cast formation with chronic inflammatory cells in the interstitium, and acute glomerular injury, align with the well- documented nephrotoxic effects of gentamicin reported in previous studies (28). In contrast, Groups I, which represent the negative control groups, showed normal kidney parameters without any abnormalities. Group IV showed similar tubular degeneration and chronic inflammatory cell presence in the interstitium compared to Group III, but without glomerular injury. This suggests that the extract may have a protective effect on glomerular function. A finding consistent with the previous work which reported the nephroprotective effects of various plant extracts against glomerular injury (31). Group V, demonstrated mild glomerular injury, tubular cast formation, and mild chronic inflammatory cells in the interstitium, indicating some kidney damage and inflammation, although less severe than in Group III. Group VI showed focal fibrosis and mild chronic inflammatory cells in the interstitium, suggesting scarring and inflammation, but without acute glomerular injury. Similar observations were made by other study

investigating the protective effects of natural compounds against chemical induced kidney tissue damage (31). As reported in previous study, some of the fern species like *Drynaria quercifolia*, consists of naringin, a flavonoid compound, which has been reported to protect against kidney injury by reducing oxidative stress, inflammation, and apoptosis (programmed cell death) in the kidneys (32).

Effect of AB extract on serum ALP, AST, and ALT

The Table 4, represents the serum concentrations of three enzymes, ALP, AST and ALT in different treatment groups. Group II, which received treatment with Gentamicin, exhibited a significant ($p < 0.001$), increased in ALP, AST, and ALT levels compared to the control group. This suggests that Gentamicin administration had a detrimental effect on liver function, as indicated by the elevated levels of these enzymes. In Group IV, V, and VI, which received different doses of the tested extract along with Gentamicin, significant improvements ($p < 0.001$), in ALP, AST levels were observed compared to the Group II. Moreover, Group III which received a combination of Ascorbic acid and Gentamicin, showed higher significant decreased ($p < 0.001$) in ALP, AST levels when compared to the Gentamicin-only group. These findings suggested that the addition of Ascorbic acid to Gentamicin treatment had a protective effect on the liver.

Table 4. Data representing level of serum ALP, AST, ALT in different groups of treatment

Experimental Group		Serum concentration (mg/dl) of		
		ALP	AST	ALT
Group I	Negative Control (Distilled water)	433.86 ± 14.23 ^{###}	62.06 ± 4.51 ^{###}	32.15± 12.21 [#]
Group II	Gentamicin	889.82±12.348 ^{***}	151.08 ±8.898 ^{***}	102.59± 6.46 ^{***}
Group III	Ascorbic acid + Gentamicin	378.61±13.108 ^{***###}	118.10 ± 9.76 ^{***###}	75.54 ± 6.59
Group IV	125mg/kg extract + Gentamicin	750 ± 11.07 ^{***###}	139.69 ± 5.12 ^{***#}	73.59± 19.54
Group V	250mg/kg extract + Gentamicin	717.79± 12.19 ^{***###}	122.30 ± 5.41 ^{***###}	86.93 ± 5.6
Group VI	500mg/kg extract + Gentamicin	685.99 ± 5.23 ^{***###}	129.37 ± 7.32 ^{***###}	76.98 ± 4.36

Note: Data expressed as mean ± standard deviation (n=6). One –way ANOVA followed by a post hoc LSD test was used for comparison between different groups. * Significant change in comparison with the control group at *p< 0.05, **p< 0.01, ***p< 0.001, # significant change in comparison with the GM group at #p< 0.05, ##p< 0.01, ###p< 0.001

In certain cases of prolonged nephrotoxicity, there can be secondary effects on the liver due to the systemic effects of renal dysfunction. If the kidneys are unable to adequately excrete waste products and toxins, it can put additional stress on the liver, leading to alterations in liver biochemical parameters. These changes may include elevated liver enzymes such as ALT, AST, , ALP and bilirubin levels.(33) In present study, similar results were observed in Table 4, after the administration of Gentamicin had a detrimental effect on liver function, as indicated by the significant increase in the levels of three enzymes (ALP, AST, and ALT) in Group II compared to the control group. This implies that Gentamicin treatment alone caused indirect effect in liver through due to nephrotoxicity. This indirect effect on the liver due to gentamicin –induced nephrotoxicity aligns with previous studies emphasizing the interconnectedness of kidney and liver function(34). However, the subsequent treatment groups showed improvements in liver function compared to Group II. In Group IV, V, and VI, which received

different doses of the tested extract along with Gentamicin, significant improvements in ALP and AST levels were observed. This suggests that the tested extract had a protective effect on the liver and helped mitigate the adverse effects caused by Gentamicin induced nephrotoxicity. Additionally, Group III, which received a combination of Ascorbic acid and Gentamicin, showed significant decreases in ALP and AST levels compared to the Gentamicin-only group, Table 4. This finding suggests that the addition of Ascorbic acid to Gentamicin treatment had a further protective effect on liver function. This supports the ideas that ascorbic acid may have a protective effect on liver function, consistent with studies that have highlighted its antioxidant properties and ability to mitigate oxidative stress –induced liver damage (35).

Effect of AB extract on liver weight

As shown in Table 5, there observed that, the treatments employed in this study did not have a significant impact on the percentage change in liver weight relative to body weight.

Table 5. Data representing the % weight of rat liver in different group of treatment

Experimental Group		Weight of liver of body weight (%) liver weight
Group I	Negative Control (Distilled water)	3.61±0.55
Group II	Gentamicin	3.59±0.72
Group III	Ascorbic acid + Gentamicin	4.01±0.06
Group IV	125 mg/kg extract + Gentamicin	4.03±0.69
Group V	250 mg/kg extract + Gentamicin	3.60±0.04
Group VI	500 mg/kg extract + Gentamicin	3.50±0.13

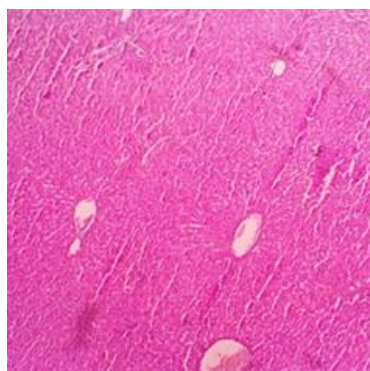
The Table 5 showed, that the treatments did not have a significant impact on the percentage change in liver weight relative to body weight, indicating that the treatments did not cause significant alterations in liver size.

Effect of AB extract on Liver tissue

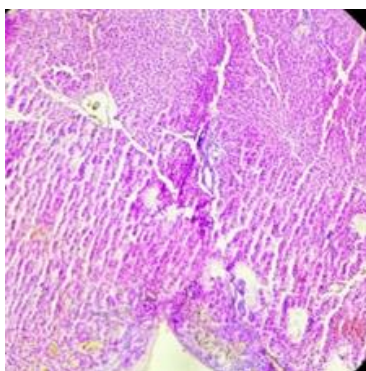
Histopathological examination of liver sections

As shown in Figure 2, Negative control (Group I) showed a normal liver architecture with no abnormalities, indicating the absence of any adverse effects. The Group II (Gentamicin only) demonstrated portal chronic inflammation, bile stasis, and degenerated hepatocytes.

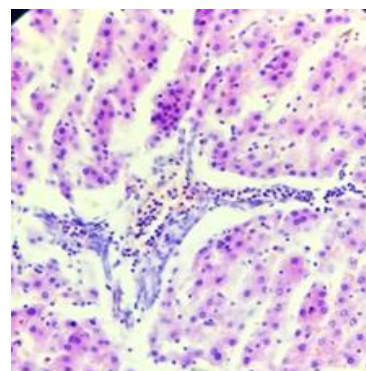
The group VI (500mg/kg extract + Gentamicin) displayed mild chronic inflammatory cells and a congested central vein. Similarly, Group III (Ascorbic acid + Gentamicin) had a normal liver architecture with mild chronic inflammation and congested blood vessels. Whereas, Group V (250mg/kg extract + Gentamicin) exhibited mild chronic inflammation in the periportal area. The Group IV (125mg/kg extract + gentamicin) showed a congested central vein, degenerated hepatocytes, and periportal chronic inflammatory cells.



Negative Control (Distilled water)



Ascorbic acid (200 mg/kg) and Genta (80 mg/kg)



Genta (80mg/kg)

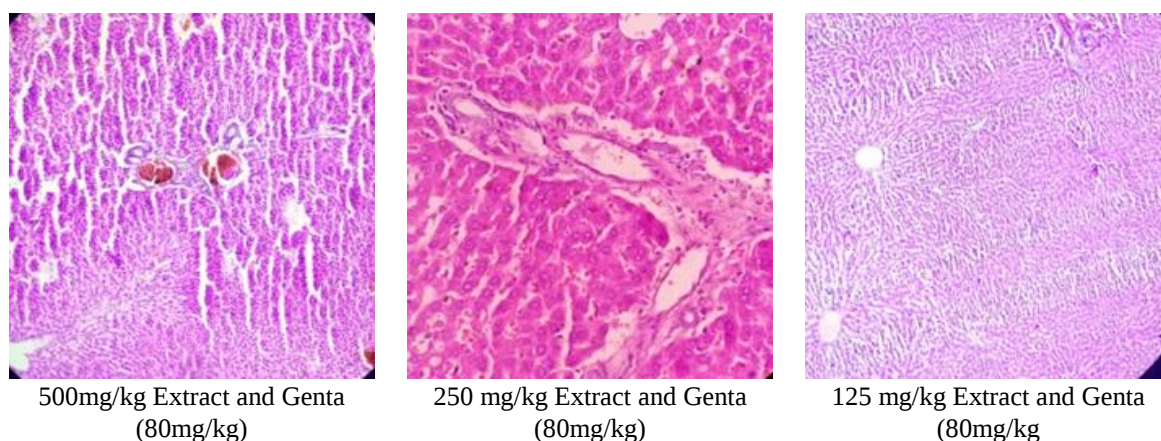


Figure 2. Effect of on liver histomorphology in various group

The results are further supported by the observations made in Figure 2, where Group I, the negative control group, showed a normal liver architecture with no abnormalities. In contrast, Group II (Gentamicin only) exhibited liver abnormalities such as portal chronic inflammation, bile stasis, and degenerated hepatocytes. However, the treatment groups that received the tested extract or Ascorbic acid along with Gentamicin (Group III, IV, V, and VI) displayed varying degrees of improvement in liver architecture, with mild chronic inflammation and congested blood vessels observed. Many fern species have been found to contain flavonoids such as quercetin and kaempferol, which have been reported to have hepatoprotective roles. (36) (40) These flavonoids have been reported in various fern species including *Drynaria quercifolia*, *Lygodium japonicum*, *Athyrium multidentatum*, and *Polypodium leucotomos*. (36) Flavonoids are known for their antioxidant and anti-inflammatory properties, which contribute to their potential hepatoprotective effects. These compounds may help protect the liver from oxidative stress and reduce inflammation (37) (39) (38).

This species investigation into nephroprotective action is novel, with no previous studies conducted. Our findings provide new insights into its hepatoprotective and nephroprotective potential, offering a valuable contribution to future therapeutic developments in

protecting liver and kidney function.

CONCLUSION

To conclude, the finding suggests that gentamicin had detrimental effect on kidney function and induced nephrotoxicity further leading to liver dysfunction. Whereas, ascorbic acid and the extract was shown to have potential renoprotective and hepatoprotective properties. The extract showed a dose-dependent reduction in (urea, creatinine, ALP, AST) biomarkers, kidney weight and showed protective effects against glomerular injury, along with protective effects on the liver, as indicated by improved enzyme levels and mitigated liver abnormalities. These findings highlight the potential of the tested extract and Ascorbic acid as therapeutic interventions to protect against Gentamicin-induced kidney along with distant organ-damage. Further research is needed to understand the underlying mechanisms and potential therapeutic applications of these interventions in renal dysfunction.

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Conflict of Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper

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الفحص الكيميائي النباتي وتقييم التأثير المحسن لمستخلص أوراق نبات *Aleuritopteris bicolor* (Roxb.) Fraser.Jenk. على تلف الكبد في نموذج فئران يعاني من سمية كلوية مستحثة بالجنتاميسين

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ملخص

الخلفية: أنواع السرخس (*Aleuritopteris bicolor* (AB)، في عائلة Pteridaceae، تستخدم تقليدياً لشفاء الجروح وعلاج أمراض مختلفة. الهدف: أجريت هذه الدراسة لتقييم إمكانية استخراج أوراق الإيثانول المائية (AB) في التخفيف من السمية الكلوية الناجمة عن الجنتاميسين والسمية الكبدية في الفئران البيضاء. الأساليب والمواد: تم تحقيق هذه الدراسة من خلال إجراء اختبار كيميائي نباتي على أوراق إيثانول AB المائية يستخلص وإدارة مستخلص الإيثانول المائي لأوراق AB شفهيًا وجنتاميسين (80 ملغ/كغ/يوم) داخل الزرء ، و Lierains و Liver -eigh ، و Liver eigh ، يوم. تم استخدام SPSS الإصدار 23 لتحليل البيانات. تم تقديم النتائج على أنها متوسط الانحراف المعياري (ن = 6). تضمن التحليل الإحصائي ANOVA أحادي الاتجاه متبوعًا باختبار اختلاف أقل أهمية (LSD). **النتائج:** من الفحص الكيميائي النباتي ، تم العثور على مستخلص الإيثانول المائي في (*Aleuritopteris* (AB) ليحتوي على الفلافونويد والفينولات والسابونين والعفص. أظهر اختبار السمية الحاد سلامته حتى 5000 ملغ/كغ. أسفرت إدارة الجنتاميسين (المجموعة II) عن زيادة كبيرة ($P < 0.001$) في اليوريا (6.22 ± 154.07 ملغ/دل) ، الكرياتينين (0.51 ± 8.90 ملغ/دل) ، وحمض اليوريك (0.74 ± 3.27 ملغ/دل) ، مما يشير إلى مجموعة من العزف الكلوي. أدى المعالجة المشتركة مع حمض الأسكوربيك (المجموعة الثالثة) وجرعات متفاوتة من مستخلص اليوريتوبيريس بيكلور (AB) المجموعات IV و V و VI إلى تخفيضات كبيرة في مستويات اليوريا والكرياتينين ، مع جرعة 500 ملغ/كغ من مستخلصات AB التي تظهر أكثر التأثيرات الملحوظة ($P < 0.001$) مقارنةً بمجموعة Gentamicin-Inly. وكشف تحليل التشريح المرضي أن الجنتاميسين تسبب في تكس أنبوبي ، وتشكيل المصبوب الغروي ، والإصابة الكبدية ، في حين أن العلاج مع مستخلص AB يقلل من هذه الأضرار. بالإضافة إلى ذلك ، تسبب الجنتاميسين في زيادات كبيرة في ALP في المصل ($P < 0.001$) ، AST ($P < 0.001$) ، و ALT ($P < 0.001$) مقارنة مع المجموعة الضابطة. العلاج مع مستخلص AB قلل بشكل كبير من هذه الإنزيمات ($P < 0.001$) مقارنة مع مجموعة الجنتاميسين فقط. وأظهر التحليل النسيجي أن مجموعة الجنتاميسين كان لها التهاب في البوابة وانحطاط خلايا الكبد ، في حين أن مستخلص AB يقلل من هذه التغيرات ، مما يدعم آثارها الوقائية ضد السمية الكلوية والكبدية. **الاستنتاجات:** تشير هذه النتائج إلى أن استخراج *Aleuritopteris bicolor* يخفف بشكل فعال من السمية الكلوية الناتجة عن الجنتاميسين والسمية الكبدية في الفئران البيضاء ، مما يدل على إمكانية الاستخدام العلاجي.

الكلمات الدالة: *Aleuritopteris bicolor* ، تحليل الكيمياء النباتية ، تأثيرات الحماية الكلوية ، تأثيرات الكبد ، سمية الجنتاميسين.

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