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PROTECTIVE PROPERTIES OF ELEUSINE INDICA (*PARAGIS PLANT*) AGAINST GENTAMICIN INDUCED NEPHROTOXICITY IN RATS

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Abstract

Gentamicin is a widely used aminoglycoside antibiotic for the treatment of severe gram-negative bacterial infections; however, its clinical application is limited by its potential to induce nephrotoxicity through oxidative stress, inflammation, and renal tubular damage. This study investigated the nephroprotective potential of *Eleusine indica* (*Paragis plant*) extract against gentamicin-induced nephrotoxicity in male Wistar rats. The whole plant of *Eleusine indica* was collected, authenticated, and extracted using aqueous extraction. Male Wistar rats (180–200 g) were randomly divided into eight experimental groups, including normal control, gentamicin-treated negative control, pre-treatment, co-administration, and post-treatment groups with two different doses of the extract (250 mg/kg and 500 mg/kg). Gentamicin (100 mg/kg) was administered intraperitoneally to induce nephrotoxicity. After the experimental period, biochemical, hematological, oxidative stress, and histopathological parameters were evaluated. Results indicated that treatment with *Eleusine indica* extract improved antioxidant status by modulating catalase (CAT), glutathione (GSH), glutathione peroxidase (GPx), and malondialdehyde (MDA) levels in treated groups compared to the negative control. The extract also influenced electrolyte balance, renal function

Keywords:
Gentamicin, Eleusine indica (*Paragis plant*) and Nephrotoxicity in Rats.

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markers (urea and creatinine), and lipid profiles. Group 5, 6 and 8 showed improvements in biochemical parameters, including increases in HDL levels and reductions in triglycerides. Liver enzyme markers and hematological parameters showed minimal alterations across the groups, indicating relative systemic safety of the extract. Overall, the findings suggest that *Eleusine indica* (*Paragis plant*) possesses antioxidant and protective properties that may mitigate gentamicin-induced renal oxidative stress and associated biochemical alterations. These results support the potential use of *Eleusine indica* as a natural nephroprotective agent. However, further studies are required to elucidate its mechanisms of action and evaluate its therapeutic potential in clinical settings.

Introduction

Kidney health is of paramount importance in maintaining the body's homeostasis, as the kidneys are responsible for essential functions such as filtering blood, excreting waste products, regulating electrolytes, and maintaining blood pressure. Despite these critical roles, the kidneys are highly susceptible to damage from various toxins, including therapeutic drugs. Drug-induced nephrotoxicity is a significant clinical issue, accounting for a substantial proportion of acute kidney injury (AKI) cases in hospitalized patients (Irvine et al., 2021). Among the drugs known to cause nephrotoxicity, gentamicin, an aminoglycoside antibiotic, is particularly notorious.

Gentamicin is widely used for the treatment of severe Gram-negative bacterial infections due to its broad-spectrum activity and low cost. However, its clinical use is limited by its potential to induce nephrotoxicity, which can lead to acute tubular necrosis and subsequent kidney failure if not managed properly (Ali *et al*., 2021). The nephrotoxic effect of gentamicin is primarily mediated through the generation of reactive oxygen species (ROS), which cause oxidative stress, inflammation, and apoptosis in renal tubular cells (Randjelovic *et al*., 2017).

Given the widespread use of gentamicin and the severity of its side effects, there is a pressing need for protective strategies that can mitigate gentamicin-induced nephrotoxicity. Current strategies include dose adjustment, hydration, and the use of antioxidants and anti-inflammatory agents to reduce oxidative stress and inflammation in the kidneys (Rapa *et al.,* 2019). However, these strategies are not always effective, and the search for novel protective agents continues.

One promising avenue of research is the use of medicinal plants, which have long been used in traditional medicine for the treatment of various ailments, including kidney disorders. Among these plants, Eleusine indica (*Paragis plant*), commonly known as goosegrass, has gained attention due to its reported medicinal properties. Paragis is a

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tropical weed widely distributed in Asia, Africa, and the Americas, where it is traditionally used to treat a variety of conditions such as fever, inflammation, and infections (Palanisamy *et al.,* 2019).

Recent studies have begun to explore the potential nephroprotective properties of Paragis, focusing on its antioxidant, anti-inflammatory, and diuretic activities. These properties suggest that Paragis may have the potential to protect against gentamicin-induced nephrotoxicity, making it a candidate for further investigation in this context (Akinmoladun *et al*., 2020).

Gentamicin-induced nephrotoxicity remains a significant challenge in clinical practice, particularly in the treatment of severe bacterial infections. While the nephrotoxic effects of gentamicin are well-documented, effective preventive strategies are still limited. The development of nephroprotective agents that can be co-administered with gentamicin to reduce its toxic effects on the kidneys is of critical importance. Traditional medicinal plants, such as Paragis, offer a potential source of novel nephroprotective agents, but their efficacy and mechanisms of action need to be scientifically validated.

Chemicals and reagents

All chemicals that is (Gentamicin, Phenol, 4–aminoantipyrine, 4–chlorophenol, Adrenaline, Hydrogen peroxide (H_2O_2), Sulphuric acid (H_2SO_4), Potassium permanganate ($KMnO_4$), Trichloroacetic acid (TCA). Picric acid, Sodium hydroxide (NaOH), Sodium hypochlorite, Phosphate buffer, Carbonate buffer, Diethanolamine buffer, Hydrochloric acid (HCl), Sodium nitrate, Sodium benzoate, Sodium chloride (NaCl), Magnesium chloride ($MgCl_2$), Copper sulphate, Potassium iodide, Sodium potassium tartrate, α-ketoglutarate / α-oxoglutarate, L-aspartate, L-alanine, ATP (Adenosine triphosphate), NAD^+ / NADH and Lactate) and reagents (Cholesterol assay reagent, HDL precipitating reagent, Triglyceride working reagent, Biuret reagent Bromocresol green (BCG) reagent, Diazotized sulphanilic acid reagent, Urease reagent, Griess reagents, Ellman's reagent (DTNB), Thiobarbituric acid (TBA) reagent, Nitrate reductase enzyme reagent, LDH reagent, AST and ALT reagents, ALP reagent, Standard solutions) used in the study was purchased from a local pharmaceutical store in Dutsin-Ma.

Sample collection and Preparation

The Eleusine indica (*Paragis plant*) was collected from a natural habitat from Sabuwa local farm in Sabuwa local government area of Katsina State. The sample was identified and authenticated at the Plant Science and Biotechnology Department Laboratory, Federal University Dutsin-Ma with identification No. FUDMA/PSB/00088. The whole plant, including leaves, stems, and roots, was thoroughly washed at room temperature and ground into a fine powder with a mortar and pestle before being extracted. The

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powdered plant material was then subjected to extraction using water as a solvent. The extraction was performed using a water bath at 50°C over 5 days. The experiment was conducted at the Federal University Dutsin-Ma, Katsina State, Department of Biochemistry and Molecular Biology Laboratory.

Ethical guidelines

The study was conducted following ethical guidelines for the Care and Use of Laboratory Animals of the National Institute of Health (National Institute of Health, 2011), United States.

Research Design

The study employed Completely Randomized Design (CRD) experimental research design using a controlled animal model. The research was conducted in a laboratory setting to ensure precise control over the experimental conditions. The study was designed to assess the nephroprotective effects of Paragis extract in rats subjected to gentamicin-induced nephrotoxicity. Rats were randomly assigned to different groups as follows:

Group 1 (Normal rats) receive normal saline.

Group 2 (negative control) rats administered gentamicin (100 mg/kg, intraperitoneally) once daily for 20 days.

Group 3 (rats given Paragis extract (250mg/kg, orally) once daily for 10 days and there after treated with gentamicin (100 mg/kg, intraperitoneally) for 10 days.

Group 4 (rats given Paragis extract (500mg/kg, orally)) once daily for 10 days and there after treated with gentamicin (100 mg/kg, intraperitoneally) once daily for 10 days.

Group 5 (rats co-administered Eleusine indica (Paragis plant) extract (250mg/kg, orally)) and (100mg/kg, intraperitoneally) gentamicin for 20 days daily.

Group 6 (rats co-administered Eleusine indica (Paragis plant) extract (500mg/kg, orally) and (100mg/kg, intraperitoneally) gentamicin for 20 days daily.

Group 7 (rats given gentamicin (100mg/kg, intraperitoneally) once daily for 10 days and there after treated with Paragis extract (250 mg/kg, orally) for 10 days.

Group 8 (rats given gentamicin (100mg/kg, intraperitoneally) once daily for 10 days and there after treated with Paragis extract (500 mg/kg, orally) for 10 days.

Biochemical Analysis

At the end of the 20 days of the feeding trial, the animals were weighed and sacrificed after adequate anaesthetization with chloroform. Blood was collected into EDTA treated and plain tubes. Plasma /serum was obtained by blood centrifugation at 1500 g for 15 min and frozen until analysis is required (Kim, 2016).

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Statistical Analysis

The data were expressed as mean ± standard deviation (SD). Statistical analysis was performed using one-way analysis of variance (ANOVA) followed by post-hoc Tukey's test to determine significant differences between the groups. A p-value of less than 0.05 was considered statistically significant.

Results

From Table 1: Group 4 showed significant increase ($p>0.05$) in CAT level when compared to group 1 and 2 (Normal and Negative control), while there was significant difference in Groups 3, 4, 5, and 6 when compared to Group 2. Group 3, 4, 6, and 7 showed significant decrease in GPX levels when compared to the Normal control (Group 1), while only Groups 3 and 8 differed significantly when compared to the Negative control (Group 2). SOD levels showed that there was no significant difference in all the test groups when compared to the Normal and Negative control. Groups 3, 4, and 8 displayed significant increase ($p<0.05$) in GSH levels when compared to the Negative control. Whereas Group 5, 6 and 7 showed significant decrease respectively when compared to the Normal control. Group 7 exhibits significant increase $p<0.05$ in MDA levels when compared to both the Normal and Negative control.

Table 1: Antioxidant protective potential of Eleusine indica *(Paragis plant*) extract against gentamicin-induced nephrotoxicity in male rats.

GROUP	CAT (u/mg)	GSH (u/ml)	GPX (u/ml)	MDA (u/mg)
Group 1 (normal control)	0.69±0.02[a]	40.80±5.51[b]	22.80.0.92[a]	6.00±1.26[a]
Group 2 (negative control)	0.61±0.02[a]	15.60±4.39[a]	15.00±148[a]	14.00±0.06[a]
Group 3 (pre 250mg)	0.69±0.03[a]	38.60±6.38[a]	16.40±3.14[a]	7.80±0.12[a]
Group 4 (pre 500mg)	0.79±0.00[a]	43.30±11.44[a]	21.60±2.24[a]	7.80±0.33[a]
Group 5 (co-adm;250mg)	0.71±0.0.01[a]	13.40±1.17[a]	17.80±2.69[a]	12.64±1.02[a]
Group 6 (co-adm;500mg)	0.71±0.01[a]	16.00±2.20[a]	22.00±4.44[a]	10.90±1.86[a]
Group 7 (post adm;250mg)	0.74±0.00[a]	17.60±2.62[a]	22.40±2.4[a]	7.22±0.29[a]

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GROUP	CAT (u/mg)	GSH (u/ml)	GPX (u/ml)	MDA (u/mg)
Group 8 (post adm;500mg)	0.65±0.02[a]	41.00±2.06[a]	19.00±2.10[a]	8.01±0.63[a]

Values are Means ± SEM for four replicates per group. Values with the same superscript alphabet are not significantly different

Key:

CAT: Catalase; GSH: Glutathione reductase; GPx: Glutathione Peroxidase; MDA: Malondialdehyde

Table 2: indicated that sodium levels in Group 4 and 5 showed significant decrease p>0.05 when compared to the Normal control, while group 4 decreased significantly when compared to the negative control. Potassium levels of Group 4 and 5 show the lowest respectively when compared to both the normal and negative controls (Group 1 and 2). High chloride levels was observed Groups 4, 5, and 6 compared to normal and negative control groups. Bicarbonate (HCO_3^-) levels in Group 4 reduced significantly p>0.05 when compared to the Negative control group. Group 4 and 5 increased significantly p<0.05 in urea level, while Groups 3, 6, 7, and 8 showed significant decrease p>0.05 when compared to the normal and negative control groups. Group 4 and 5 of creatine level showed significant difference when compared to the normal and negative control group.

Table 2: Effect on Electrolytes Levels of Eleusine indica (*Paragis plant*) Extract against gentamicin-induced nephrotoxicity in male rats.

GROUP	Na^+ (mmol/l)	K^+ (mmol/l)	Cl^- (mmol/l)	HCO_3^- (mmol/l)	Urea (mmol/l)	Creatinine (mmol/l)
Group 1 (normal control)	1.45±0.93[c]	5.80±0.07[b]	1.03±0.51[c]	20.80±1.24[ab]	5.72±0.33[a]	88.40±2.60[a]
Group 2 (negative control)	1.43±0.86[bc]	5.80±0.84[b]	1.00±1.21[c]	22.60±0.87[b]	4.72±0.10[a]	92.20±2.01[a]
Group 3 (pre 250mg)	1.42±0.51[bc]	5.45±0.23[b]	1.00±0.40[c]	23.20±1.39[b]	7.30±0.82[ab]	101.40±5.50[a]
Group 4 (pre 500mg)	1.36±2.03[a]	4.66±0.34[a]	94.60±2.11[a]	18.00±1.05[a]	15.58±2.08[c]	103.6±10.81[c]
Group 5 (co-adm;250mg)	1.39±2.75[ab]	4.76±0.15[a]	96.20±2.15[ab]	20.60±1.60[ab]	11.00±3.06[b]	110.80±7.48[bc]
Group 6 (co-adm;500mg)	1.44±0.58[c]	5.62±0.06[b]	99.60±0.51[b]	21.40±0.51[b]	6.76±0.13[a]	129.0±1.52[ab]
Group 7 (post adm;250mg)	1.46±0.32[c]	5.78±0.10[b]	1.02±0.51[c]	21.80±0.58[b]	5.24±0.23[a]	102.60±2.71[a]

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GROUP	Na^+ (mmol/l)	K^+ (mmol/l)	Cl^- (mmol/l)	HCO_3^- (mmol/l)	Urea (mmol/l)	Creatinine (mmol/l)
Group 8 (post adm;500mg)	1.45±0.68^c	5.80±0.17^b	1.02±0.37^c	23.60±0.40^b	4.84±0.24^a	94.60±2.32^a

Values are Means ± SEM for four replicates per group. Values with the same superscript alphabet are not significantly different at ($p< 0.05$).

Table 3: revealed that groups 3, 4 and 5 showed significant decrease in TP levels $p>0.05$, when compared to the normal and negative control groups (1 and 2), while groups 6 and 7 differed significantly when compared to the negative control (group 2).
In the ALB levels, only group 5 showed a significant decrease when compared to group 1 and 2. While groups 5, 6, 7, and 8 displayed significant increase $p<0.05$ in ALP levels when compared to the normal and negative control groups. AST levels of groups 5 and 6 decreased significantly $p>0.05$ when compared to the normal and negative control. Meanwhile, ALT, TB and CB showed no significant difference in all the groups when compared to the normal and negative control. Group 8 of LDH level decreased significantly when compared to the normal and negative control.

Table 3: Effect Eleusine indica (*Paragis plant*) Extract on Liver Enzymes in gentamicin-induced nephrotoxicity in male rats

GROUPS	TP (g/l)	ALB (g/l)	ALP (g/l)	AST (g/l)	ALT (u/l)	TB (mg/dl)	CB (mg/dl)	LDH (u/l)
Group 1 (normal control)	69.20±1.16^{cde}	33.20±0.74^b	55.60±1.70^a	14.80±0.37^{bc}	6.00±0.32^{ab}	0.62±0.04^a	0.16±0.03^{ab}	77.40±0.93^{bc}
Group 2 (negative control)	73.20±0.86^e	34.40±0.68^b	53.80±4.22^a	14.40±0.81^{bc}	5.00±0.32^a	0.62±0.06^a	0.14±0.03^{ab}	75.80±1.36^{bc}
Group 3 (pre 250mg)	61.80±2.42^a	33.60±0.93^b	49.80±1.72^a	15.60±0.51^c	4.80±0.49^a	0.56±0.05^a	0.10±0.00^a	77.40±0.93^{bc}
Group 4 (pre 500mg)	61.80±2.42^a	33.60±0.93^b	49.80±1.72^a	15.60±0.51^c	4.80±0.49^a	0.56±0.05^a	0.10±0.00^a	77.40±0.93^{bc}
Group 5 (co-adm;250 mg)	63.60±0.51^{ab}	29.60±1.54^a	76.20±5.30^c	10.60±3.44^{ab}	5.20±1.56^a	0.58±0.07^a	0.14±0.03^{ab}	80.60±4.24^c
Group 6	65.20±0.86^{abc}	32.40±0.51^b	68.80±1.66^b	9.40±0.51^a	5.20±0.37^a	0.62±0.06^a	0.18±0.02^b	80.60±1.08^c

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GROUPS	TP (g/l)	ALB (g/l)	ALP (g/l)	AST (g/l)	ALT (u/l)	TB (mg/dl)	CB (mg/dl)	LDH (u/l)
(co-adm;500 mg)								
Group 7 (post adm;250 mg)	67.20±0.66^{bcd}	32.40±0.75^{b}	76.00±2.17^{c}	17.00±0.71^{c}	8.00±0.55^{b}	0.64±0.08^{a}	0.14±0.03^{ab}	79.60±2.46^{bc}
Group 8 (post adm;500 mg)	71.20±1.02^{de}	35.00±0.55^{b}	66.00±1.76^{b}	14.60±0.81^{bc}	5.80±0.66^{a}	0.66±0.09^{a}	0.18±0.04^{b}	66.60±1.08^{a}

Values are Means ± SEM for four animals per group. Values with the same superscript alphabet are not significantly different at ($p<0.05$)

Key:
TP: Total protein; ALB: Albumin; ALP: Alkaline phosphatase; AST: Aspartate aminotransferase; ALT: Alanine aminotransferase; TB: Total bilirubin; CB: Conjugated bilirubin; LDH: Lactate dehydrogenase.

The result in Table 4: shows that groups 3, 4 and 7 differed significantly in TC levels when compared to the normal and negative control (group 1 and 2), while group 5, 6 and 8 showed significant difference in TC levels when compared to the negative control. Groups 5, 6, 7, and 8 displayed a significant decrease in TG level when compared to the normal and negative control.
HDL levels of group 2, 3, 4, 5, 6, 7 and 8 increased significantly $p<0.05$ when compared to the negative control, while group 7 increased significantly when compared to the normal control.

Table 4: Lipid Profile of Eleusine indica (*Paragis plant*) Extract against gentamicin-induced nephrotoxicity in male rats

GROUPS	TC (mg/dl)	TG (mg/dl)	HDL (mg/dl)
Group 1 (normal control)	1.11±1.40^{b}	80.40±7.30^{a}	19.80±1.20^{ab}
Group 2 (negative control)	89.60±2.50^{a}	76.20±4.78^{a}	16.00±0.55^{a}
Group 3 (pre 250mg)	1.25±0.87^{c}	87.60±1.47^{a}	23.60±0.68^{bc}
Group 4 (pre 500mg)	1.25±0.87^{c}	87.60±1.47^{a}	23.60±0.68^{bc}
Group 5 (co-adm;250mg)	1.18±1.63^{bc}	1.04±1.72^{b}	22.00±0.84^{bc}
Group 6 (co-adm;500mg)	1.21±0.87^{bc}	1.29±1.08^{c}	23.00±0.45^{bc}
Group 7 (post adm;250mg)	1.24±2.58^{c}	1.30±2.69^{c}	25.60±1.33^{c}
Group 8 (post adm;500mg)	1.31±8.00^{b}	1.08±12.07^{b}	22.00±3.12^{bc}

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Values are Means ± SEM for four replicates per group. Values with the same superscript alphabet are not significantly different at ($p<0.05$)
Key:
TC: Total cholesterol; TC: Triglyceride; HDL: High density lipoprotein.

The result in Table 5: shows that group 4, 5 and 7 of WBC increased significantly when compared to the negative control. Group 4, 7 of LYM showed significant decrease when compared to the normal control. Meanwhile PCV, HB, NEU, MON, BAS, EOS and PLT showed no significant difference across the various groups when compared to the normal and negative control.

Table 5: Heamatological Parameters of Paragis (*Eleusine indica*) extract against gentamicin-induced nephrotoxicity in male rats

GROUP	WBC (10^3/Ul)	PCV (%)	HB (g/dl)	NEU (%)	LYM (%)	MON (%)	BAS (%)	EOS (%)	PLT (10^3/Ul)
Group 1 (normal control)	1.06±2.08^{ab}	29.12±0.78^{a}	9.32±0.20^{a}	6.60±0.20^{a}	93.44±0.17^{b}	0.08±0.04^{a}	0.26±0.05^{a}	0.46±0.09^{a}	1.34±3.00^{a}
Group 2 (negative control)	1.01±1.28^{a}	29.54±0.21^{a}	9.44±0.24^{a}	6.94±1.03^{a}	91.48±0.52^{ab}	0.20±0.03^{a}	0.30±0.03^{a}	0.52±0.05^{a}	1.30±4.67^{ab}
Group 3 (pre 250mg)	1.07±3.47^{ab}	28.80±1.31^{a}	9.24±0.42^{a}	5.80±0.40^{a}	93.08±0.37^{ab}	0.20±0.03^{a}	0.30±0.03^{a}	0.58±0.02^{a}	1.29±7.07^{abc}
Group 4 (pre 500mg)	1.14±4.22^{b}	29.22±0.23^{a}	10.32±0.68^{a}	7.84±1.09^{a}	90.86±0.87^{a}	0.12±0.05^{a}	0.32±0.15^{a}	0.50±0.14^{a}	1.20±2.72^{ab}
Group 5 (co-adm;250 mg)	1.12±2.05^{b}	29.20±0.46^{a}	9.36±0.31^{a}	5.78±0.16^{a}	91.84±0.93^{ab}	0.16±0.05^{a}	0.30±0.10^{a}	0.48±0.18^{a}	1.25±1.57^{abc}
Group 6 (co-adm;500 mg)	1.08±3.91^{ab}	28.96±0.53^{a}	9.40±0.30^{a}	7.40±0.98^{a}	91.94±0.84^{ab}	0.20±0.06^{a}	0.14±0.03^{a}	0.58±0.19^{a}	1.25±1.16^{abc}
Group 7 (post adm;250 mg)	1.14±2.01^{b}	30.12±0.36^{a}	9.86±0.12^{a}	6.62±0.40^{a}	91.12±0.78^{a}	0.18±0.05^{a}	0.22±0.05^{a}	0.54±0.03^{a}	1.18±3.71^{a}
Group 8 (post adm;500 mg)	1.03±2.44^{a}	27.88±1.18^{a}	9.38±0.31^{a}	7.30±1.01^{a}	91.14±0.70^{a}	0.14±0.05^{a}	0.30±0.03^{a}	0.60±0.07^{a}	1.19±1.03^{ab}

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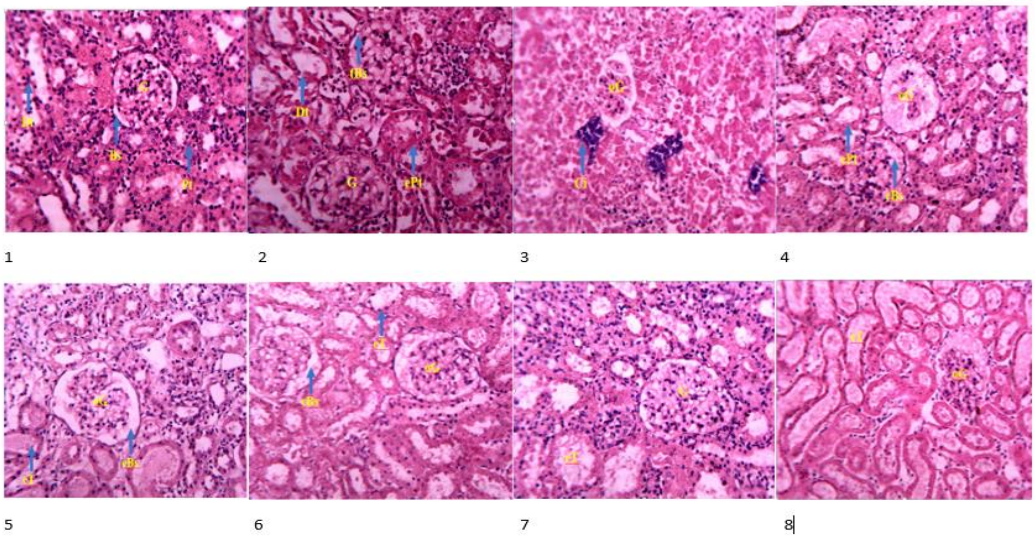
Values are Means ± SEM for four replicates per group. Values with the same superscript alphabet are not significantly different at ($p<0.05$)

Key:

WBC: White blood cell; PCV: Packed cell volume; HB:Hemoglobin; NEU: Neutrophils; LYM: Lymphocyte; MON: Monocyte; BAS:Basophils; EOS: Eosinophils; PLT: Platelet

Plate 1: Kidney section with relatively normal histoarchitectural features, Glomerulus (G); Proximal tubules (Pt); Distal tubules (Dt); Bowman space (Bs). Plate 4.2: Kidney section with relative histoarchitectural distortion, Glomerulus (G); enlarged Proximal tubules (ePt); Distal tubules (Dt); tight Bowman space (tBs), Plate 4.3: Kidney section with relative histoarchitectural distortion, obliterated Glomerulus (oG); Cellular infiltration (Ci), Plate 4.4: Kidney section with relative histoarchitectural distortion, obliterated Glomerulus (oG); enlarged Proximal tubules (ePt); enlarged Bowman space (eBs), Plate 4.5: Kidney section with relative histoarchitectural distortion, obliterated Glomerulus (oG); enlarged tubules (eT); enlarged Bowman space (eBs), Plate 4.6: Kidney section with relative histoarchitectural distortion, obliterated Glomerulus (oG); enlarged tubules (eT); enlarged Bowman space (eBs), Plate 4.7: Kidney section with relative histoarchitectural distortion, Glomerulus (G); enlarged tubules (eT), Plate 4.8: Kidney section with relative histoarchitectural distortion, obliterated Glomerulus (oG); enlarged tubules (eT) (H&E x250).

Plate 1: Histopathological changes in kidney tissues of gentamicin-induced nephrotoxicity rats treated with *Paragis*



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Discussion

Gentamicin is a well-known nephrotoxic antibiotic that induces oxidative stress in renal cells, leading to cellular damage. This toxicity is mediated by the generation of reactive oxygen species (ROS), which deplete antioxidant defense mechanisms and increase lipid peroxidation.

The observed increase in CAT levels in Group 4 suggests a potential enhancement of a key antioxidant enzyme by *Paragis* extract, which is crucial for the detoxification of hydrogen peroxide (Halliwell & Gutteridge, 2015). A higher CAT activity could indicate a better ability to scavenge ROS. The varying effects on GPX and GSH levels across groups are complex. While some groups showed a decrease in GPX, which is an enzyme involved in reducing lipid hydroperoxides, an increase in GSH in Groups 3, 4, and 8 is a positive indicator. GSH is a vital non-enzymatic antioxidant that directly neutralizes free radicals and acts as a cofactor for GPX (Lushchak, 2012). *Paragis* extract boost GSH levels by increasing its production, reducing its depletion, and supporting its regeneration in the body. The lack of significant difference in SOD levels across all groups is unexpected, as SOD is typically one of the primary enzymes involved in dismutating superoxide radicals into less harmful forms (Jomova *et al.*, 2024). The significant increase in MDA in Group 7 indicates elevated lipid peroxidation, a hallmark of oxidative stress and cellular damage (Ayala *et al*., 2014). The fact that *Paragis* extract in other groups did not lead to a significant increase in MDA, and in some cases improved other antioxidant markers, suggests a potential protective effect, although the exact mechanisms and optimal dosage (represented by different groups) need further elucidation. The mixed results highlight the complex nature of antioxidant defense systems and the need for a balanced approach in interpreting their markers.

Gentamicin-induced nephrotoxicity primarily affects the renal tubules, leading to impaired reabsorption and secretion functions, which manifest as electrolyte imbalances and elevated markers of renal dysfunction such as urea and creatinine (Rapa *et al.,* 2019). The observed decreases in sodium and potassium in Groups 4 and 5, along with altered chloride and bicarbonate levels, suggest a disruption in renal tubular function, potentially indicating damage to the ion transport mechanisms in these specific groups. This is consistent with gentamicin's known mechanism of action, which includes damage to the proximal convoluted tubules leading to electrolyte wasting (El Moualij *et al*., 2020). The significant increases in urea and creatinine in Groups 4 and 5 are strong indicators of impaired glomerular filtration and overall kidney dysfunction. Urea and creatinine are waste products primarily excreted by the kidneys, and their accumulation in the blood signifies reduced renal clearance (Rehmat *et al.,* 2025). Conversely, the significant decrease in urea in Groups 3, 6, 7, and 8, when compared to the control groups, is a very

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promising finding. This suggests that *Paragis* extract in these specific groups may be effectively mitigating the gentamicin-induced kidney damage, allowing for better filtration and excretion of waste products. This differential effect across groups underscores the importance of dosage and preparation of the extract. The implications are that certain *Paragis* extract formulations or dosages may offer protection against gentamicin-induced renal impairment by preserving kidney function.

While gentamicin is primarily nephrotoxic, high doses or prolonged exposure can also exert some degree of hepatotoxicity, indicated by alterations in liver enzyme levels (El Moualij *et al*., 2020). Liver enzymes such as ALP, AST, and ALT are commonly used markers of hepatocellular injury and cholestasis (Shaab & Abulghasem, 2025). Total protein and albumin levels reflect the synthetic function of the liver (Kalas, 2021).

The significant decreases in TP and ALB levels in certain groups (3, 4, 5, 6, 7) could indicate impaired hepatic synthetic function, possibly due to a systemic effect of gentamicin. The significant increases in ALP levels in Groups 5, 6, 7, and 8 suggest potential cholestasis or liver cell damage. However, the lack of significant differences in ALT, TB, and CB, which are more specific markers of hepatocellular necrosis and bilirubin metabolism, is reassuring and suggests that severe hepatotoxicity was likely not a major outcome across most groups. These observed effects, particularly in Groups 5 and 6 where *Paragis* extract was co-administered with gentamicin, may reflect a synergistic or additive interaction between the plant extract and the drug. Such interaction could modify biochemical responses either by enhancing protective antioxidant mechanisms or by influencing metabolic pathways involved in liver function. The significant decrease in AST in Groups 5 and 6 is an interesting finding; AST is present in various tissues including the heart, muscle, and kidney, so a decrease could be attributed to complex interactions, possibly including synergistic effects between treatments or reduced cellular leakage in those specific groups (Lala & Minter, 2023). The significant decrease in LDH in Group 8 suggests a reduction in overall tissue damage, as LDH is a general marker of cellular injury (Farhana & Lappin, 2023).

Nephrotoxicity and systemic inflammation can influence lipid metabolism, leading to dyslipidemia (Agrawal *et al.,* 2018). Kidney damage can result in alterations in lipoprotein synthesis and catabolism.

The varying significant differences in TC levels across groups suggest an influence on cholesterol metabolism, which could be related to the direct effects of the extract. The significant decrease in TG levels in Groups 5, 6, 7, and 8 is a positive outcome, as elevated triglycerides are a risk factor for cardiovascular disease and can be exacerbated by systemic stress or kidney dysfunction (Anni *et al.*, 2021). The most promising finding is the significant increase in HDL levels in almost all treated groups (Groups 2-8), especially Group 7 showing an increase compared to the normal control. HDL is often referred to as

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"good cholesterol" due to its role in reverse cholesterol transport, which helps remove excess cholesterol from tissues and protect against atherosclerosis. This suggests that *Paragis* extract may have beneficial effects on lipid profiles, potentially counteracting some of the metabolic derangements associated with gentamicin toxicity and potentially offering cardiovascular protection.

Gentamicin can cause hematological alterations, including bone marrow suppression and immune dysregulation, although its primary target is the kidneys (El Moualij *et al*., 2020). Hematological parameters are crucial indicators of overall health, immune response, and potential systemic toxicity.

The significant increase in WBC in Groups 4, 5, and 7 could indicate an inflammatory response or an immune system activation. While an increase in WBC can sometimes be a sign of infection or inflammation, in the context of nephrotoxicity, it might represent a non-specific immune response to cellular damage. The significant decrease in lymphocytes in Groups 4 and 7 compared to the normal control is noteworthy, as lymphocytes are key components of the adaptive immune system. A decrease in lymphocytes could suggest immunosuppression or a redistribution of immune cells in response to the insult. The consistent lack of significant difference in PCV, HB, NEU, MON, BAS, EOS, and PLT across most groups suggests that *Paragis* extract, at the tested doses, did not overtly cause anemia, neutropenia, or thrombocytopenia, which are positive indicators of its safety regarding these specific hematological aspects. However, the changes in WBC and lymphocytes warrant further investigation to understand the specific immune modulating effects of *Paragis* extract in the context of gentamicin toxicity.

Plate 4.1 describes kidney architecture with relatively normal histoarchitectural features, showing intact glomeruli (G), proximal tubules (Pt), distal tubules (Dt), and well-defined Bowman's space (Bs). This represents a healthy renal morphology consistent with normal renal physiology and homeostasis (Tervaert *et al*., 2010).

Plate 4.2 reveals enlarged proximal tubules and tight Bowman's space, suggesting early signs of tubular injury and glomerular filtration impairment. Plate 4.3 shows obliterated glomeruli and cellular infiltration, indicative of glomerulonephritis or inflammatory response, which aligns with findings in toxin-induced nephropathy models (Watanabe *et al*., 2025).

While Plate 4.4 to Plate 4.6 depict obliterated glomeruli, enlarged tubules, and Bowman's space, which signify advanced stages of glomerular damage, potentially leading to tubulointerstitial fibrosis and chronic kidney disease (CKD) (Lim *et al*., 2017). On the other hand, Plate 4.7 and 4.8 continue to show enlarged tubules with or without glomerular obliteration. This may reflect compensatory tubular hypertrophy or ischemic damage, consistent with nephrotoxic effects observed in models exposed to heavy metals or NSAIDs (Orr & Bridges, 2017). These distortions across multiple sections suggest the test

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subject(s) experienced renal structural compromise, possibly due to exposure to nephrotoxic agents, oxidative stress, or chronic inflammation.

Obliteration of glomeruli and tubular changes such as dilation and atrophy are well-documented consequences of toxic insult or ischemic conditions. Studies show that oxidative stress, pro-inflammatory cytokines, and fibrotic changes all contribute to the degradation of renal histoarchitecture (Rapa *et al.,* 2019). Moreover, research into protective agents like medicinal plants or antioxidants often uses similar histological markers to evaluate kidney damage and recovery (Lee *et al*., 2024).

Conclusion

Eleusine indica (*Paragis plant*) extract protects against gentamicin-induced kidney damage in male rats by reducing oxidative stress (increasing catalase and glutathione) and lowering urea levels. It also improves HDL cholesterol without major safety concerns, though some inconsistent effects on electrolytes, liver enzymes, and white blood cells highlight dose-dependent complexities. Histological findings confirm a spectrum of renal protection. *Paragis plant* shows promise as a natural renoprotective agent, warranting further mechanistic and optimization studies.

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