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Research Paper

Evaluation of Nephroprotective Activity of Polyherbal extract (Tinospora cordifolia and Cucurbita pepo) against Gentamicin Induced Nephrotoxicity

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ABSTRACT

The present study aimed to evaluate the nephroprotective potential of a methanolic polyherbal extract of Tinospora cordifolia and Cucurbita pepo against Gentamicin-induced nephrotoxicity in experimental rats. Nephrotoxicity was induced using gentamicin, which led to significant renal impairment as evidenced by decreased body weight, altered urinary parameters, elevated serum creatinine and blood urea nitrogen (BUN), and reduced creatinine clearance. Oxidative stress was confirmed by increased malondialdehyde (MDA) levels and decreased antioxidant enzymes such as superoxide dismutase (SOD), catalase (CAT), and reduced glutathione (GSH). Histopathological studies revealed tubular necrosis, epithelial degeneration, and disruption of normal renal architecture. Treatment with the standard drug silymarin significantly restored biochemical and antioxidant parameters. The methanolic polyherbal extract exhibited dose-dependent nephroprotective activity by improving renal function, reducing oxidative stress, and preserving tissue architecture. The high-dose extract showed effects comparable to silymarin. The nephroprotective effect is attributed to the presence of bioactive phytoconstituents with antioxidant and cytoprotective properties.

INTRODUCTION

Acute Kidney Injury (AKI) is a serious clinical condition characterized by a rapid decline in renal function over a short period, typically hours to days. It results in the inability of the kidneys to efficiently filter metabolic waste products and maintain fluid, electrolyte, and acid–base balance. Clinically, AKI is identified by a sudden rise in serum creatinine, increased blood urea nitrogen (BUN), reduced urine output (oliguria), and disturbances in electrolytes such as potassium and sodium. If not managed promptly, AKI can progress to life-threatening complications

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including metabolic acidosis, hyperkalemia, fluid overload, and multi-organ dysfunction (1).

AKI can be classified into three major categories based on its etiology: pre-renal (due to decreased renal blood flow), intrinsic or intra-renal (due to direct damage to renal tissues), and post-renal (due to obstruction of urinary outflow). Among intrinsic causes, drug-induced nephrotoxicity represents a significant and preventable contributor to acute renal damage. The kidneys are particularly vulnerable to toxic injury because of their high blood flow, active tubular transport mechanisms, and ability to concentrate substances within the tubular lumen (2).

Drug Induced Nephrotoxicity- It occurs when pharmacological agents or their metabolites cause structural and functional damage to renal tissues. Various therapeutic classes are implicated, including aminoglycoside antibiotics, non-steroidal anti-inflammatory drugs (NSAIDs), chemotherapeutic agents such as cisplatin, immunosuppressants like cyclosporine, and radiographic contrast media. These agents can induce renal injury through multiple mechanisms such as oxidative stress, inflammation, altered renal hemodynamics, mitochondrial dysfunction, and direct tubular toxicity. Fig 1 illustrates the mechanism of Gentamicin induced nephrotoxicity (3).

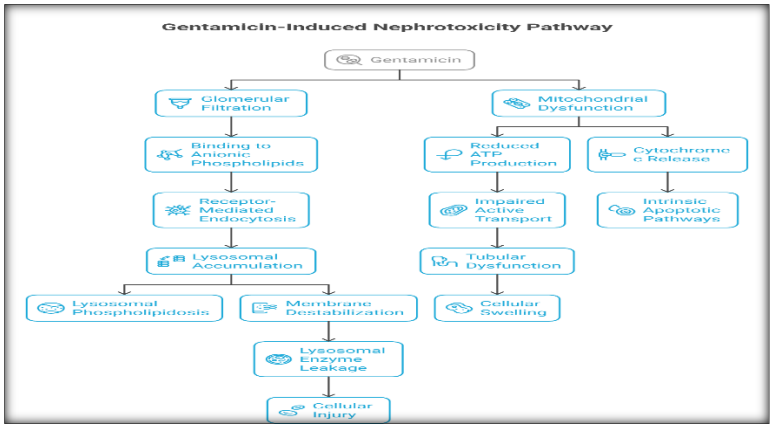

Figure 1: Gentamicin induced nephrotoxicity pathway

Tinospora cordifolia (Guduchi) is a well-known medicinal plant in Ayurveda with significant pharmacological properties, including antioxidant, anti-inflammatory, and nephroprotective effects. It contains bioactive compounds such as alkaloids, glycosides, flavonoids, and phenolics that contribute to its therapeutic potential. *Cucurbita pepo* (pumpkin) is a nutritionally and medicinally important plant widely used in traditional medicine. It is rich in bioactive compounds such as flavonoids, phenolics, carotenoids, vitamins, and essential fatty acids, which contribute to its antioxidant and anti-inflammatory properties (4-5).

1. MATERIAL & METHODS

A. Test formulation

The flowers of *Cucurbita Pepo* and leaves of *Tinospora cordifolia* (Guduchi) were collected from …The flowers of *Cucurbita Pepo* and leaves of *Tinospora cordifolia* were washed under tap water and dried in the air under the shade at room temperature and converted to a coarse powder and stored in an airtight container. For the physicochemical investigation, 100 g of dried powder was successively extracted with different solvents such as petroleum ether, chloroform, and methanol in increasing order of polarity using Soxhlet apparatus. The extracts were concentrated under reduced pressure using rotary flash evaporator, and the residues were dried in a desiccator and stored for further use (6).

B. Preliminary Phytochemical Screening

The aqueous, chloroform and methanolic extracts of the drug were subjected to initial phytochemical screening. Tests were based on observable color changes or fluorescence. Results were recorded as Present (+) or Absent (–). These tests revealed the presence of many bioactive secondary metabolites, which might be accountable for their medicinal characteristics. Methods adopted for initial qualitative phytochemical examinations of the drug extracts were as per the standard procedures (7).

C. Dose Selection and Schedule

For efficacy study dose was selected based on the acute oral toxicity study (rats) and therapeutic dose (1000 mg) of polyherbal extract in adults. The dose for rats was calculated by extrapolating the human dose to animals (100 mg/kg) based on the body surface area ratio by referring to the standard table of Paget and Barnes and CCSEA. Distilled water was used as a vehicle. Fresh test drug solutions of poly-herbal extracts were prepared at two different concentrations of 100 and 200 mg/kg in distilled water and administered in suitable volumes orally based on the body weight of animals with the help of an oral gavage tube sleeved to a syringe (8-9).

D. Acute Oral Toxicity

An acute oral toxicity study was carried out as per OECD guideline 423. The male Wistar albino rats (non-pregnant, nulliparous) were used for the study. Distilled water was used as the vehicle to administer the test drug. The animals were administered a dose of 2000 mg/kg through oral gavage and observed for 14 days for signs of toxicity, including changes in behavior, fur condition, salivation, tremors, or lethargy (10).

E. Experimental Animals

Healthy adult male albino rats of Wistar strain weighing about 170-200g were obtained from…... Animals were maintained under standard laboratory conditions with normal dark and light cycles and room temperature (27 ± 2ºC). All procedures used in the study were reviewed and approved by the Institutional Animal Ethics Committee (Approval No: …..)

Experimental Design:

Animal to be used: 30 Albino Wistar Rats (Male)
Total Duration of the Study: 30 days
Animals will be acclimatized for at least 7 days before the start of the experiment, with free access to standard pellet diet and water ad libitum.
Nephrotoxicity will be induced in Groups II–V by Gentamicin 30 mg/kg, i.p., once daily for 10 consecutive days (Day 1–10). The polyherbal extract (PHE) and standard drug will be administered orally (p.o.) once daily for 30 days, starting on the same day as the first gentamicin injection. Towards the end of the study (Day 29–30), animals will be placed in metabolic cages for 24-hour urine collection. On Day 30, blood will be collected under light anesthesia from the retro-orbital plexus; animals will then be euthanized with ketamine (80–100 mg/kg, i.p.), and kidneys will be isolated for biochemical and histopathological evaluation (11).

Table 2: Treatment schedule for evaluation of nephroprotective activity of the polyherbal extract selected for the present study in gentamicin rat model.

Groups	Treatment	Dose Level	Animals	Total Animals
G-I	Normal Control	Normal saline solution, p.o.	6 Rats	
G-II	Experimental Control	Gentamicin, [30 mg/kg, i.p.]	6 Rats	
G-III	Standard Control	Gentamicin, [30 mg/kg, i.p.]	6 Rats	

		+ Nephroprotective Drug[Silymarin (100 mg/kg, oral)		30 Albino Wistar Rats (Male)
G-IV	Test group Polyherbal low dose	Gentamicin, [30 mg/kg, i.p.] + Polyherbal extract low dose (200 mg/kg, p.o.)	6 Rats	
G-V	Test group Polyherbal high dose	Gentamicin, [30 mg/kg, i.p.] + Polyherbal extract low dose (400 mg/kg, p.o.)	6 Rats	

F. Biochemical analysis:

i. **Blood collection:** Under mild isoflurane anesthesia, 2 mL of blood was collected through the retro-orbital route in anticoagulant-coated and hematocrit tubes which were centrifuged at 5000 rpm for 15 min to separate serum and plasma and stored at −20°C for further biochemical analysis.

ii. **Urine collection:** On the last day of treatment, the urine samples were collected by placing the animals in metabolic cages overnight and provided with water ad libitum. The next day, urine was collected, and stored in a deep freezer (−20°C) until further analysis for protein urea (12).

iii. Change in body weight and urine volume

On the 1st, 15th and 30th day, the body weight was measured to evaluate the changes in the body weight from the initial weight. The change in volume of urine was measured on day 1, 15th and 30th day (13).

iv. Estimation of Creatinine and Protein urea

Creatinine level in urine and serum was estimated by using BA-400 autoanalyzer, and protein levels in urine were estimated by the Coomassie Brilliant Blue G-250 method and the absorbance was read at 595 nm (14).

v. Antioxidant assay

Superoxide dismutase levels (SOD) using the hemolysate were estimated and the absorbance was read at 570 nm. The levels of blood urea nitrogen (BUN) were determined by using the ERBA Mannheim Urea-Bun Determination Kit method and absorbance was read at 340 nm (15).

BUN [mg/dL] = Urea (mg/dL)/2.1428)

Malondialdehyde (MDA) levels in plasma were estimated and absorbance was read at 535 nm (16). The catalase (CAT) level in serum samples was analyzed using spectrophotometric determination of hydrogen peroxide (H_2O_2) which forms a stable complex with ammonium molybdate that absorbs at 405 nm. CAT activities are expressed as kilo unit per liter (kU/L) (17) .

vi. Histopathology

Excised kidneys were fixed in a 10% neutral buffered formalin for a period of 24 h and were processed for dehydration using absolute ethanol, cleaned in xylene, and embedded in paraffin. The sectioning was made using microtome apparatus at a thickness of 4 µm and stained with eosin and hematoxylin. All histopathological evaluations were performed in a blinded fashion to ensure objective assessment of tissue samples. The

histopathological changes of each section were observed and photographed (45x and 100x) using a light microscope equipped with a digital camera (18).

vii. Statistical analysis

The data was expressed as Mean ± SEM. Results were analyzed in comparison with Group II statistically by one-way analysis of variance by Dunnett's multiple t test and post hoc test using Graph Pad Prism version 6.01 (GraphPad Software, LLC, Boston, MA, USA).

2. RESULT & DISCUSSION

A. Test Formulations: Table 3 describes about results of phytochemical screening.

Table 3: Results of Phytochemical screening of Different Polyherbal extracts

S. No.	Test		Aqueous	Chloroform	Methanol
1.	**Alkaloids**				
	A.	Dragandroff's test	++	+	+++
	B.	Mayer's test	++	+	+++
	C.	Wagner's test	++	+	+++
	D.	Hager's test	+	+	++
2.	**Tannins and Phenols**				
	A.	5% $FeCl_3$	+++	+	+++
	B.	Lead acetate	++	+	+++
		Acetic acid	++	-	++
		Dilute HNO3	++	-	++
		Dil. Potassium per magnet	+++	+	+++
3.	**Coumarin**				
	A.	Aromatic	++	+	++
4.	**Steroids**				
	A.	Salkowski reaction	+	++	++
	B.	Liberman reaction	+	++	++
5.	**Saponins**				
	A.	Foam test	+++	-	++
6.	**Glycosides**				
	A.	Borntrager's test	++	+	+++
7.	**Flavonoids**				
	A.	Lead acetate	++	+	+++
	B.	NaOH	+++	+	+++
	C.	Sulphuric acid	++	+	++
	D.	Ethanol + HCl+ mg turnings	++	-	+++
8.	**Terpenoids**				
	A.	Extract+ chloroform+ conc. Sulfuric acid	+	+++	++

B. Acute Toxicity study: No clinical signs of toxicity and mortality were observed at 2000 mg/kg inferring that the drug is safe (table 4). Feed intake was monitored throughout the 14-day observation period. Animals maintained consistent feed intake from day 1 to day 14, indicating normal appetite and physiological function in the absence of test substance-related toxicity. During the efficacy study, an initial low dose (e.g., one-tenth or one-twentieth of the MTD) was administered to ensure safety and observe potential biological effects. To establish a dose-dependent response relationship, a higher dose of 300 mg/kg was subsequently tested.

Table 4: Acute toxicity body: weight change and feed consumption

Day (g)	Day 0	Day 7	Day 14
Body weight (g)	191.48 ± 1.97	193.36± 2.97	196.29± 3.26
Feed Consumption (g)	95.32	97.24	100.65

C. Evaluation of nephroprotective activity

1. Effect on physical Parameters: Body weight

At the beginning of the study (Day 1), no significant difference in body weight was observed among all experimental groups ($P>0.05$) as evident in Table 5, indicating uniform distribution of animals. On Day 15, the gentamicin-treated group (Group II) showed a significant decrease in body weight compared to the control group. In contrast, the silymarin-treated group (Group III) showed a moderate increase. The polyherbal extract-treated groups showed dose-dependent improvement, with Group IV and Group V, the latter being significantly higher than Group II ($P<0.05$).

Table 5: Effect of PHE extract on body weight measured at different days

Group	Treatment	Dose level	Body wt. (g)		
			1st Day	15th Day	30th Day
I	Control	Normal saline 3ml/kg, p.o.	180 ± 5.8	195 ± 6.9	210 ± 7.3
II	Experimental Control	Normal Saline (3ml/kg, p.o.) + Gentamicin (30mg/kg, i.p.	182 ± 6.4	170 ± 5.6	158 ± 6.9
III	Standard Control	Gentamicin (30 mg/kg, i.p.) + Silymarin (100 mg/kg, oral)	181 ± 5.4	185 ± 6.7	195 ± 6.8
IV	Polyherbal extract (low dose)	Gentamicin (30 mg/kg, i.p.) + PHE extract (200 mg/kg, oral)	180 ± 5.4	178 ± 5.3	185 ± 6.4
V	Polyherbal extract (high dose)	Gentamicin (30 mg/kg, i.p.) + PHE extract (400 mg/kg, oral)	182 ± 6.1	188 ± 5.3	200 ± 7.4

2. Effect on Urinary Parameters

A. Effect on Urine Volume

No significant difference in urine volume was observed among groups on Day 1 (P>0.05) (Table 6). Gentamicin significantly increased urine volume on Day 15 and Day 30 (P<0.01), indicating impaired renal function. Silymarin treatment significantly reduced urine volume compared to the gentamicin group, showing protective effects. The polyherbal extract showed dose-dependent improvement, with the high dose approaching normal values and the low dose showing moderate recovery.

Table 6: Effect of PHE extract on urine volume measured at different days against Gentamicin induced Nephrotoxicity

Group	Treatment	Dose level	Urine Volume (ml/24 h)		
			Day 1	Day 15	Day 30
I	Control	Normal saline 3ml/kg, p.o.	8.4 ± 0.5	8.6 ± 0.4	8.8 ± 0.4
II	Experimental Control	Normal Saline (3ml/kg, p.o.) + Gentamicin (30mg/kg, i.p.	8.5 ± 0.5	11.8 ± 0.7	15.5 ± 0.9
III	Standard Control	Gentamicin (30 mg/kg, i.p.) + Silymarin (100 mg/kg, oral)	8.6 ± 0.4	9.8 ± 0.6	10.5 ± 0.6
IV	Polyherbal extract (low dose)	Gentamicin (30 mg/kg, i.p.) + PHE extract (200 mg/kg, oral)	8.5 ± 0.5	10.5 ± 0.6	12.8 ± 0.7
V	Polyherbal extract (high dose)	Gentamicin (30 mg/kg, i.p.) + PHE extract (400 mg/kg, oral)	8.4 ± 0.4	9.6 ± 0.5	10.9 ± 0.6

D. Effect on Creatinine and Creatinine Clearance levels- No significant changes were observed in Group 1 in Creatinine clearance and urine creatinine levels (P>0.05) as evident in table 7. By Day 30, the gentamicin group exhibited a further significant decline in creatinine clearance and urine creatinine levels. Silymarin markedly restored both parameters. Notably, the high-dose polyherbal extract group showed values comparable to the standard treatment while the low-dose group demonstrated moderate recovery.

Table 7: Effect of PHE extract on Urine Creatinine and Creatinine Clearance level against Gentamicin Induced Nephrotoxicity

Group	Treatment	Dose level	Urine Creatinine (mg/dL)	Creatinine Clearance (ml/min)
I	Control	Normal saline 3ml/kg, p.o.	26± 0.32	0.87 ± 0.04
II	Experimental Control	Normal Saline (3ml/kg, p.o.) + Gentamicin (30mg/kg, i.p.	11± 0.43	0.30 ± 0.03
III	Standard Control	Gentamicin (30 mg/kg, i.p.) + Silymarin (100 mg/kg, oral)	20± 0.56	0.68 ± 0.05
IV	Polyherbal extract (low dose)	Gentamicin (30 mg/kg, i.p.)	16± 0.42	0.52 ± 0.04

		+ PHE extract (200 mg/kg, oral)		
V	Polyherbal extract (high dose)	Gentamicin (30 mg/kg, i.p.) + PHE extract (400 mg/kg, oral)	21± 0.24	0.70 ± 0.05

3. Effect on Serum Parameters

A. Effect on Blood Urea Nitrogen and Serum Creatinine level

The effect of various treatments on serum creatinine and blood urea nitrogen (BUN) levels in experimental rats demonstrated significant alterations in renal function as evident in table 8. The control group (Group I) showed normal serum creatinine and BUN levels, indicating normal kidney function. In contrast, the Gentamicin-treated group (Group II) exhibited a marked elevation in serum creatinine and BUN levels ($p<0.001$), confirming severe nephrotoxicity. The standard treatment group (Group III) receiving silymarin showed significant restoration of both serum creatinine and BUN, indicating strong nephroprotective activity. The polyherbal extract at low dose (Group IV) produced moderate improvement, reducing serum creatinine and BUN levels ($p<0.001$). In contrast, the high-dose group (Group V) showed a more pronounced effect, significantly lowering serum creatinine and BUN levels ($p<0.001$), demonstrating significant dose-dependent nephroprotective activity.

Table 8: Effect of PHE extract on Gentamicin induced Nephrotoxicity on BUN and Serum Creatinine levels (Mean ± SEM) (n=6)

Group	Treatment	Dose level	BUN (mg/dl) Mean ±SEM	Serum Creatinine (mg/dl) Mean ± SEM
I	Control	Normal saline 3ml/kg, p.o.	30.50±0.42	0.75±0.01
II	Experimental Control	Normal Saline (3ml/kg, p.o.) + Gentamicin (30mg/kg, i.p.	71.34±0.34*	2.20 ±0.03
III	Standard Control	Gentamicin (30 mg/kg, i.p.) + Silymarin (100 mg/kg, oral)	36.83±0.23#	0.53±0.03
IV	Polyherbal extract (low dose)	Gentamicin (30 mg/kg, i.p.) + PHE extract (200 mg/kg, oral)	52.65±0.32#	0.92±0.02
V	Polyherbal extract (high dose)	Gentamicin (30 mg/kg, i.p.) + PHE extract (400 mg/kg, oral)	40.34±0.12#	0.63±0.12

B. Effect on total protein and albumin level

Gentamicin treatment significantly increased serum creatinine and BUN levels ($p<0.001$), indicating severe nephrotoxicity. The control group maintained normal levels, confirming normal renal function. Silymarin significantly restored serum creatinine and BUN, demonstrating strong nephroprotective activity. The polyherbal extract showed dose-dependent improvement, with the high dose producing effects comparable to the standard and the low dose showing moderate protection.

Table 9: Effect of PHE extract on Gentamicin induced changes in Total Protein and Albumin levels (Mean ± SEM) (n=6)

Group	Treatment	Dose level	Total Protein (g/dL)	Albumin (g/dL)
I	Control	Normal saline 3ml/kg, p.o.	7.75±0.06	5.15±0.05
II	Experimental Control	Normal Saline (3ml/kg, p.o.) + Gentamicin (30mg/kg, i.p.	3.12±0.16	2.27±0.06
III	Standard Control	Gentamicin (30 mg/kg, i.p.) + Silymarin (100 mg/kg, oral)	7.03±0.07	5.07±0.04
IV	Polyherbal extract (low dose)	Gentamicin (30 mg/kg, i.p.) + PHE extract (200 mg/kg, oral)	6.53±0.09	4.10±0.13
V	Polyherbal extract (high dose)	Gentamicin (30 mg/kg, i.p.) + PHE extract (400 mg/kg, oral)	6.98±0.11	4.72±0.10

4. *In-vivo* antioxidant studies

Gentamicin treatment significantly increased MDA levels and decreased SOD, CAT, and GSH ($p<0.001$), indicating severe oxidative stress and lipid peroxidation (Table 10). Silymarin significantly reduced MDA and restored antioxidant enzymes to near-normal levels, demonstrating strong protective effects. The polyherbal extract showed dose-dependent activity, with the low dose producing moderate improvement in oxidative stress parameters. The high-dose extract markedly reduced MDA and restored SOD, CAT, and GSH levels comparable to silymarin, indicating strong antioxidant and nephroprotective potential.

Table 10: Effect of PHE extract on Gentamicin induced Nephrotoxicity changes on the levels of different anti-oxidant markers

Group	Treatment	Dose level	MDA	SOD	CAT	GSH
I	Control	Normal saline 3ml/kg, p.o.	5.79 ± 1.37	8.66 ± 0.74	0.103 ± 0.009	10.10 ± 2.37
II	Experimental Control	Normal Saline (3ml/kg, p.o.) + Gentamicin (30mg/kg, i.p.	11.32 ± 0.55$^{\$\$\$}$	3.76 ± 0.47$^{\$\$\$}$	0.047 ± 0.009$^{\$\$\$}$	2.53 ± 1.06$^{\$\$\$}$
III	Standard Control	Gentamicin (30 mg/kg, i.p.)	6.46 ± 0.96***	7.55 ± 1.41**	0.98 ± 0.009**	8.07 ± 1.45***

		+ Silymarin (100 mg/kg, oral)				
IV	Polyherbal extract (low dose)	Gentamicin (30 mg/kg, i.p.) + PHE extract (200 mg/kg, oral)	7.80 ± 1.00***	6.50 ± 1.34**	0.073 ± 0.005*	6.21 ± 1.16**
V	Polyherbal extract (high dose)	Gentamicin (30 mg/kg, i.p.) + PHE extract (400 mg/kg, oral)	6.90 ± 0.86***	7.10 ± 1.21**	0.091 ± 0.009**	7.77 ± 1.35***

5. Histopathology Study

Histopathological examination revealed significant structural changes correlating with biochemical findings. The control group showed normal renal architecture with intact glomeruli and tubules. Gentamicin-treated rats exhibited severe damage, including tubular necrosis, epithelial degeneration, inflammation, and glomerular disruption. These findings confirm acute renal injury induced by gentamicin. Silymarin-treated group showed marked improvement with near-normal glomeruli and minimal inflammation. The low-dose polyherbal extract group showed moderate protection with partial restoration and mild degeneration. The high-dose group demonstrated significant improvement with nearly normal glomeruli and minimal tubular damage. Histological features in the high-dose group were comparable to the standard, indicating strong nephroprotective activity.

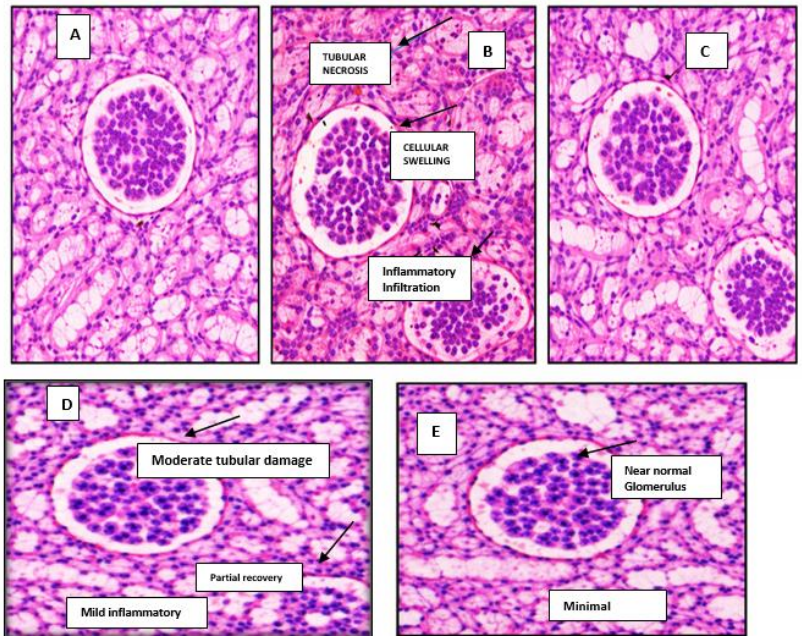

Fig 8.13: Histopathology of Kidney

A: Normal Control, B: Gentamicin Induced Nephrotoxicity, C: Gentamicin + Silymarin, D: Low dose PHE, E: High dose PHE

DISCUSSION

The present study demonstrates that gentamicin induces nephrotoxicity through oxidative stress and free radical generation. The observed increase in MDA levels and decrease in antioxidant enzymes confirms lipid peroxidation and depletion of endogenous defense systems. Treatment with *Tinospora cordifolia* significantly attenuated these effects, suggesting its strong antioxidant potential. The phytoconstituents present in the plant, particularly flavonoids and phenolic compounds, may contribute to free radical scavenging and cellular protection. The improvement in biochemical parameters and histopathological features further supports the nephroprotective role of the plant extract.

CONCLUSION

Tinospora cordifolia exhibits significant nephroprotective activity against gentamicin-induced renal damage. The protective effect is primarily mediated through antioxidant mechanisms, restoration of renal function, and preservation of kidney architecture. This study supports the potential use of *Tinospora cordifolia* as a natural therapeutic agent for preventing drug-induced nephrotoxicity.

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