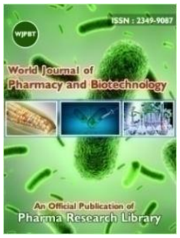

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Effect of Tectona Grandis on Cisplatin-Induced Nephrotoxicity

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A B S T R A C T

Cisplatin, a widely used chemotherapeutic agent, is known for its nephrotoxic effects, which significantly limit its clinical utility. The study investigates the nephroprotective effects of the ethanolic extract of Tectona grandis (EETG) against Cisplatin-induced nephrotoxicity in rats. Cisplatin treatment resulted in elevated serum glucose and cholesterol levels, indicative of renal dysfunction. Administration of EETG (250 mg/kg and 500 mg/kg) significantly reduced these biochemical markers compared to the control group, with the lower dose (250 mg/kg) showing greater efficacy in managing glucose and cholesterol levels. This study highlights the potential of EETG as a protective agent against Cisplatin-induced renal damage, emphasizing its therapeutic benefits in reducing nephrotoxicity.

Keywords: Cisplatin, nephrotoxicity, Tectona grandis, ethanolic extract, renal protection, glucose levels, cholesterol levels.

A R T I C L E   I N F O

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C O N T E N T S

1. Introduction

Nephrotoxicity, resulting from exposure to drugs or toxins, impairs kidney function, leading to elevated blood electrolytes and waste accumulation. Common causes include therapeutic agents like aminoglycoside antibiotics, chemotherapeutic drugs, NSAIDs, and chemicals such as ethylene glycol and heavy metals[1]. Nephroprotective agents, particularly medicinal plants, offer protective benefits, with species like Tribulus terrestris, Ocimum sanctum, and Aegle marmelos showing efficacy. Treatment typically involves stopping the harmful agent and may include therapies like dobutamine, norepinephrine, and diuretics(2). Traditional medicine has long used plants for kidney health, and research supports their effectiveness, revealing mechanisms and validating their therapeutic use.(3) Tectona grandis (Verbenaceae), known for its nephroprotective potential, is the focus of current studies for its protective effects against drug-induced nephrotoxicity, highlighting the importance of identifying non-toxic, cost-effective herbal remedies for kidney health. Tectona grandi, known as teak or Indian oak, is a member of the Verbenaceae family, with its leaves, bark, and whole plant used medicinally.[4]

Fig no: 1 Leaves of *Tectona grandis*

The plant contains phenols, flavonoids, glycosides, alkaloids, steroids, and fatty esters. Traditionally, it is used to treat diabetes, lipid disorders, inflammation, ulcers, and bronchitis. The bark has antihyperglycemic properties, while the root exhibits hypoglycaemic activity. Known by various vernacular names, such as sagwan in Hindi and tekku in Tamil, T. grandis holds significant therapeutic potential in traditional medicine.

2. Materials and Methods

2.1. Plant Material

2.1.1. Collection of Plant

Leaves of *Tectona grandis* was collected from local market, Nellore District, Andhra Pradesh.

1.1.2. Preparation of The Extract

The dried leaves of *Tectona grandis* were cleaned, powdered, and passed through a 40 mesh sieve. About 1000 gm of this powder was extracted with aqueous ethanol using a Soxhlet apparatus until exhaustion, and the solvent was recovered by distillation under reduced pressure. The resulting dried extract was stored in a desiccator for further experiments.

1.2. Experimental Animals

Healthy adult male Wistar rats (150-200 gm) were housed in groups of six under standard conditions, fed a standard diet, and given purified water ad libitum for one week before and during the experiments. All procedures were approved by the Institutional Animal Ethical Committee (IAEC), conducted according to current laboratory animal care guidelines and ethical guidelines for experimental pain investigation.

2.3. Drugs and Chemicals

DTNB, gentamicin, lithium, formalin, various chemicals, and estimation kits were sourced from S.D. Fine Chemicals Pvt. Ltd., Mumbai.

2.4 Instruments

Instruments used included an Analytical Auto Analyzer (Max Lyzer NB-201), UV-Visible Spectrophotometer (Shimadzu 2203), Electronic Balance (Shimadzu DS-852 J), Tissue Homogenizer (Ever shine 607), and Remi Centrifuge (KKLO-9013).

2.5 Acute Oral Toxicity Study

An acute oral toxicity study following OECD 423 guidelines used Wistar rats divided into six groups. Groups II-VI received extract doses of 100 to 5000 mg/kg, while group I received a control. The rats were observed for 24 hours to determine the LD50.

2.6. Experimental Design

2.6.1. Nephroprotective Activity

The experimental animals were randomly divided in to 5 groups (n= 6) and treated for duration of 21 days as per the treatment schedule given in table no: 3. Nephrotoxicity was induced by administration of Cisplatin (80 mg/kg I.P) daily for 7 days. Ethanolic extract of *T. grandis* was freshly suspended in CMC and administered to animals by oral feeding needle.

2.6.2. Collection of Blood and Urine Samples

Blood samples were collected from the retroorbital venous plexus without coagulant, allowed to stand for 1 hour at room temperature, and then centrifuged at 2000 rpm for 15 minutes to separate serum, which was stored for biochemical analysis. Urine was collected over 24 hours on the 21st day using metabolic cages, and its volume was measured before analyzing biochemical parameters such as urine creatinine, uric acid, and urea.

3. Results and Discussion

3.1. Pharmacological Studies

1. Acute toxicity studies
2. Nephroprotective activity

3.1.1. Acute Toxicity Studies

Acute oral toxicity studies following OECD 423 guidelines showed that the ethanolic extract of *Tectona grandis* was safe up to 5000 mg/kg, with no mortality or adverse behavioral, neurological, or autonomic effects. The LD50 was determined to be greater than 5000 mg/kg. For efficacy evaluation, 500 mg/kg was chosen as the high dose and 250 mg/kg as the low dose.

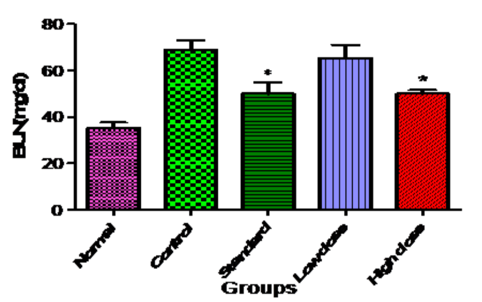
3.1.2. Nephroprotective Activity

A). Biochemical Parameters in Serum:

a). Effect on Blood Urea Nitrogen (BUN) :

Serum BUN levels were measured using an Erba BUN kit. Results indicated a significant increase in BUN levels in the control group (G-II) compared to the normal group (G-I). The high dose of the extract (G-III, 500 mg/kg) had similar effects to the normal group (G-I). The high dose of EETG (500 mg/kg) in group (G-V) significantly decreased BUN levels ($p<0.05$), while the low dose (250 mg/kg) in group (G-IV) did not show a significant reduction compared to the control group (G-II).

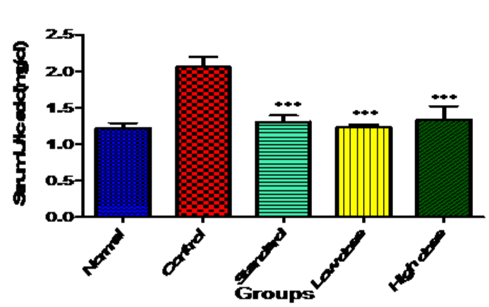
Fig no: 5 Effect of EETG on Blood Urea Nitrogen



b). Effect on Uric acid:

Serum uric acid levels, measured using an Auto span Uric acid kit, showed a significant increase in the control group (G-II) compared to the normal group (G-I). Both EETG doses (250 mg/kg and 500 mg/kg) significantly decreased serum uric acid levels ($p<0.001$) compared to the control. The high dose (500 mg/kg) in the normal group (G-III) had similar effects to the untreated normal group (G-I).

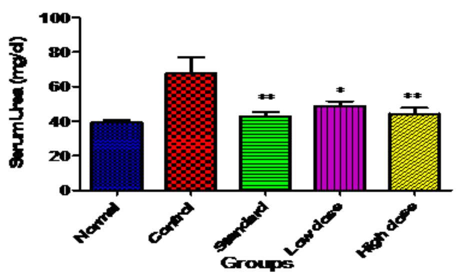
Fig no: 6 Effect of EETG on Uric acid



c). Effect on Urea:

Serum urea levels, measured with a Life Chem Urea kit, revealed a significant increase in the control group (G-II) compared to the normal group (G-I). EETG treatment resulted in a significant decrease in serum urea levels, with the high dose (500 mg/kg, G-V) showing a more pronounced reduction ($p<0.01$) compared to the low dose (250 mg/kg, G-IV, $p<0.05$). The high dose also had similar effects to the untreated normal group (G-I).

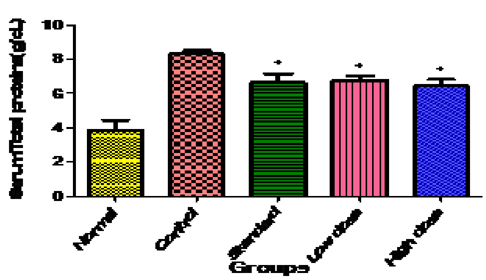
Fig no: 7 Effect of EETG on Serum Urea



d). Effect on Total Protein:

Serum total protein levels, measured with an Erba Total Protein kit, significantly increased in the control group (G-II) compared to the normal group (G-I). The high dose of EETG (500 mg/kg, G-III) had effects similar to the untreated normal group (G-I). Both EETG doses (250 mg/kg and 500 mg/kg, G-IV and G-V) significantly decreased serum total protein levels compared to the control group (G-II) ($p<0.05$).

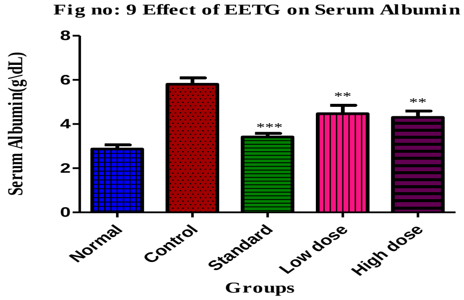
Fig no: 8 Effect of EETG on Total Protein



e). Effect on Albumin:

Serum albumin levels, measured with an Auto Span Albumin kit, significantly increased in the control group (G-II) compared to the normal group (G-I). Both EETG doses (250 mg/kg and 500 mg/kg, G-IV and G-V) significantly decreased serum albumin levels ($p<0.01$) compared to the control group. The high dose of EETG (500 mg/kg, G-III) had similar effects to the untreated normal group (G-I).

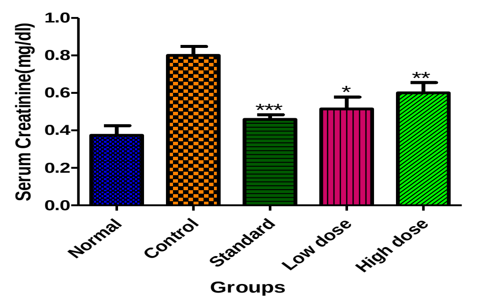
Fig no: 9 Effect of EETG on Serum Albumin



f). Effect on Creatinine:

Serum creatinine levels, measured with a Coral Creatinine kit, significantly increased in the control group (G-II) compared to the normal group (G-I). The high dose of EETG (500 mg/kg, G-III) showed effects similar to the untreated normal group (G-I). EETG at 250 mg/kg (G-IV) significantly decreased creatinine levels ($p<0.05$), while the 500 mg/kg dose (G-V) showed a more significant reduction ($p<0.01$) compared to the control group (G-II)

Fig no: 10 Effect of EETG on Serum Creatinine



3.1.3. Morphological Parameters

a). Effect on Body weight:

Body weight measurements showed a 16.7% decrease in the control group (G-II) on the 21st day, significantly lower than the normal group (G-I) ($p<0.001$). EETG treatment at 250 mg/kg (G-IV) and 500 mg/kg (G-V) resulted in 6.7% and 3.3% changes in body weight, respectively, with significant increases compared to the control ($p<0.01$ and $p<0.001$). The high dose (500 mg/kg, G-III) had effects similar to the untreated normal group (G-I).

Fig no: 11 Effect of EETG on percentage (%) Body Weight

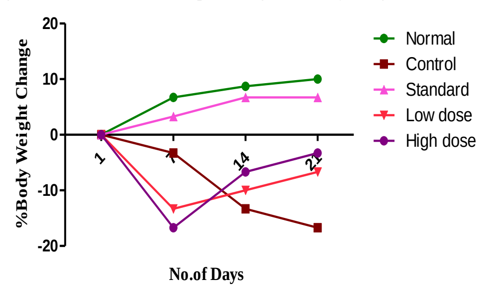
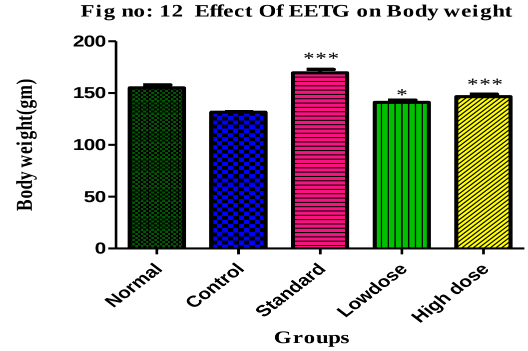


Fig no: 12 Effect Of EETG on Body weight

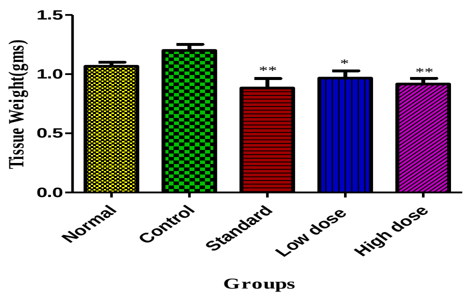


b). Effect on Kidney weight:

At the end of the study, kidney weights were significantly higher in the control group (G-II) compared to the normal group (G-I). The high dose of EETG (500 mg/kg, G-III) had effects similar to the untreated normal group (G-I).

EETG at 250 mg/kg (G-IV) and 500 mg/kg (G-V) significantly reduced kidney weight compared to the control group ($p<0.05$ and $p<0.01$, respectively).

Fig no: 13 Effect of EETG on Kidney Weights

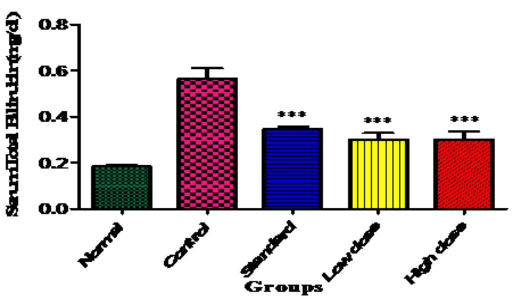


3.1.4. Non Renal Parameters

a). Effect on Total Bilirubin:

Total bilirubin levels, measured with an Erba total bilirubin kit, were significantly higher in the control group (G-II) compared to the normal group (G-I). EETG at 250 mg/kg (G-IV) and 500 mg/kg (G-V) significantly decreased total bilirubin levels ($p<0.001$) compared to the control group. The high dose of EETG (500 mg/kg, G-III) had effects similar to the untreated normal group (G-I).

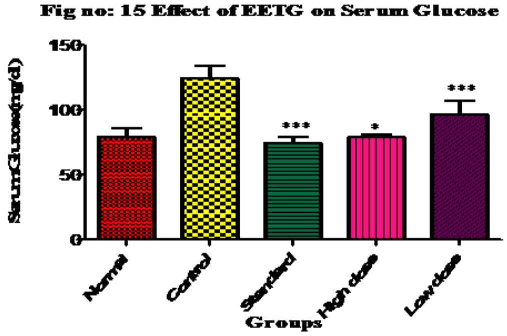
Fig no: 14 Effect of EETG on Total Bilirubin



b).Effect on Glucose:

Glucose levels, measured with an Erba Glucose kit, significantly increased in the control group (G-II) compared to the normal group (G-I). EETG at 500 mg/kg (G-III) and both doses (250 mg/kg and 500 mg/kg, G-IV and G-V) significantly reduced glucose levels compared to the control group ($p<0.001$ and $p<0.05$, respectively). Notably, the lower dose (250 mg/kg) was more effective than the higher dose in reducing glucose levels.

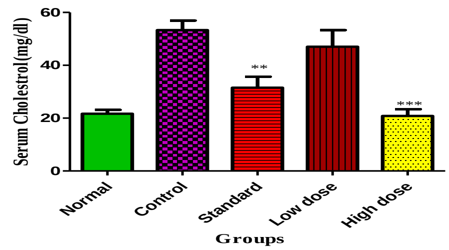
Fig no: 15 Effect of EETG on Serum Glucose



c). Effect on Cholestrol:

Cholesterol levels, measured with an Erba cholesterol kit, were significantly lower in the group treated with EETG at 250 mg/kg (G-IV) compared to the control group (G-II) ($p<0.001$). The group treated with EETG at 500 mg/kg (G-III) also showed a significant reduction ($p<0.01$), while the higher dose (G-V) did not differ significantly from the control group.

Fig no:16 Effect of EETG on Serum Cholestrol



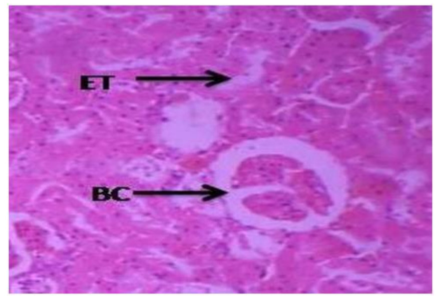


Fig.17: Photo micrograph of Kidney tissue in normal group

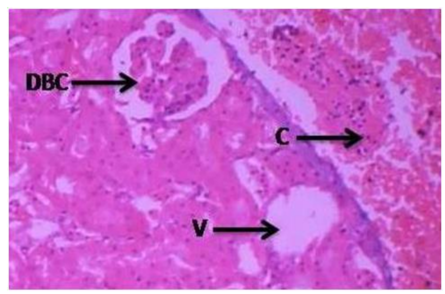


Fig.18: Photo micrograph of Kidney tissue in control group

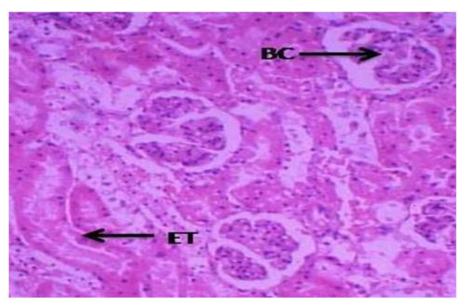


Fig.19: Photo micrograph of Kidney tissue in standard group.

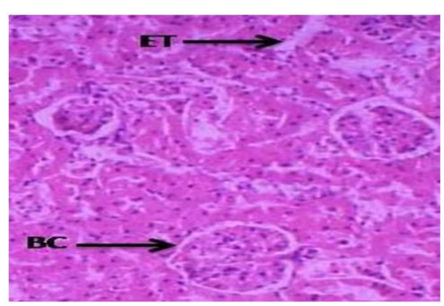


Fig.20: Photo micrograph of kidney tissue in low dose group.

Table no: 1 Treatment schedule –Evaluation of nephroprotective activity of EETG against Cisplatin induced nephrotoxicity in Wistar Rats.

S.NO	Groups	Treatment (21 days)	Purpose
I	Normal	Vehicle (1% CMC)	To serve as normal animal
II	Control	Cisplatin (80 mg/kg, i.p.)	To serve as control
III	Standard	EETG (500 mg/kg, p.o.).	To serve as standard
IV	Low dose	Cisplatin (80 mg/kg, i.p.) + EETG (250 mg/kg, p.o.)	To assess the Nephroprotective activity of EETG (at low dose)
V	High dose	Cisplatin (80 mg/kg, i.p.) + EETG (500 mg/kg, p.o.)	To assess the Nephroprotective activity of EETG (at high dose)

Table no: 2 Effect of EETG on uric acid in urine

Groups	Treatment	Uric acid (mg/dl)	% Protection
I	Normal (1% CMC)	1.73	__
II	Control cisplatin (80 mg/kg, i.p.)	4.53	__
III	Standard EETG (500 mg/kg, p.o)	1.45	__
IV	Cisplatin (80 mg/kg, i.p..) + EETG (250 mg/kg, p.o)	2.65	41.51
V	Cisplatin (80 mg/kg, i.p.) + EETG (500 mg/kg, p.o)	2.16	52.32

Table no: 3 Effect of EETG on urea in urine

Groups	TREATMENT	Urea (mg/dl)	% Protection
I	Normal (1% CMC)	17.75	__
II	Control cisplatin (80 mg/kg, i.p.)	21.25	__
III	Standard EETG (500 mg/kg, p.o)	12.5	__
IV	Cisplatin (80 mg/kg, i.p..) + EETG (250 mg/kg, p.o)	15.5	27.06
V	Cisplatin (80 mg/kg, i.p.) + EETG (500 mg/kg, p.o)	13.75	35.30

Table no: 4 Effect of EETG on creatinine in urine

Groups	Treatment	Creatinine (mg/dl)	% Protection
I	Normal (1% CMC)	13.8	__
II	Control cisplatin (80 mg/kg, i.p.)	25.2	__
III	Standard EETG (500 mg/kg, p.o)	14.4	__
IV	Cisplatin (80 mg/kg, i.p..) + EETG (250 mg/kg, p.o)	18.9	25
V	Cisplatin (80 mg/kg, i.p.) + EETG (500 mg/kg, p.o)	16.7	33.74

Table no: 5 Effect of EETG on urine volume

Groups	Treatment	Urine volume (ml)	% Protection
I	Normal (1% CMC)	3.25	__
II	Control cisplatin (80 mg/kg, i.p.)	2	__
III	Standard EETG (500 mg/kg, p.o)	3.20	__
IV	Cisplatin (80 mg/kg, i.p.) + EETG (250 mg/kg, p.o)	3.10	55
V	Cisplatin (80 mg/kg, i.p.) + EETG (500 mg/kg, p.o)	3.23	61.5

Table no: 7 Effect of EETG on body weight

Groups	Treatment	Body weight(gms)
I	Normal (1% CMC)	155.0±2.887
II	Control cisplatin (80 mg/kg, i.p.)	131.5±0.5627#
III	Standard EETG (500 mg/kg, p.o)	169.5±3.354***
IV	Cisplatin (80 mg/kg, i.p.) + EETG (250 mg/kg, p.o)	141.0±2.309*
V	Cisplatin (80 mg/kg, i.p.) + EETG (500 mg/kg, p.o)	146.5±2.377***

Table no: 8 Effect of EETG on kidney weight

Groups	Treatment	ON 21ST DAY Kidney Weight (gms)
I	Normal (1% CMC)	1.06±0.03
II	Control cisplatin (80 mg/kg, i.p.)	1.20±0.05###
III	Standard EETG (500 mg/kg, p.o)	0.88±0.07**
IV	Cisplatin (80 mg/kg, i.p.) + EETG (250 mg/kg, p.o)	0.96±0.06*
V	Cisplatin (80 mg/kg, i.p.) + EETG (500 mg/kg, p.o)	0.91±0.04**

4. Conclusion

The nephroprotective effects of T. grandis ethanolic Plant extract was evaluated against Cisplatin induced Nephrotoxicity. The study assessed serum renal markers (creatinine, urea, uric acid, total protein, albumin, BUN), non-renal markers (cholesterol, glucose, total bilirubin), kidney and body weights, antioxidant parameters (LPO, GSH, catalase), and histopathology. The extract significantly decreased renal markers, improved morphological parameters, and increased body weights. It demonstrated antioxidant activity by reducing LPO levels and enhancing CAT and GSH levels in kidney homogenates. Moreover, T. grandis showed potential nephroprotection against lithium-induced nephrogenic diabetes insipidus by potentially inhibiting ENaC on distal nephrons, thus preventing lithium accumulation. Histopathological findings supported its protective effects on kidney tissues.

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