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PHYTOCHEMICAL ANALYSIS AND PHARMACOLOGICAL EVALUATION OF ETHANOL EXTRACT OF FRUITS OF *GREWIA TILIAEFOLIA* FOR NEPHROPROTECTIVE ACTIVITY

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Keywords:

Nephroprotective, *Grewia tiliaefolia* , Cisplatin, Serum markers

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ABSTRACT: Aim: The present study was undertaken to screen the phytochemicals present in fruits of *Grewia tiliaefolia* and to evaluate the potential role of these fruits in the amelioration of cisplatin-induced nephrotoxicity in male Albino rats. **Materials and methods:** Ethanol extract of Fruits of *Grewia tiliaefolia* was prepared by hot extraction method. The prepared ethanol extract was subjected to preliminary phytochemical evaluation followed by TLC, HPTLC, HPLC and GC-MS analysis. The nephroprotective potential of the extract was screened at 200 and 400mg/kg b. w. in both curative and prophylactic regimens in male Albino rats. Nephrotoxicity was induced by single intraperitoneal injection of cisplatin at a dose of 5 mg/kg b.w. The nephroprotective activity was assessed by determining serum markers, urinary parameters, lipid peroxidation and antioxidant levels and his to pathological studies in renal tissue. **Results:** Upon preliminary phytochemical screening, the ethanol extract showed the presence of Proteins, flavonoids, Tannins, Terpenoids. HPTLC analysis resulted in a fingerprint of extract showing the presence of 14 compounds. TLC and HPLC revealed the presence of quercetin, and GC-MS analysis showed the presence of 80 different phytochemicals. Pharmacological studies revealed that administration of extract significantly attenuated the cisplatin- induced nephrotoxicity remarkably by restoring the biochemical and oxidative stress markers in both curative and prophylactic regimens in dose-dependent manner. **Conclusion:** Thus, the findings of the present study provided the phytochemical profile and validated the ethnomedicinal use of fruits of *Grewia tiliaefolia* as a renoprotective agent.

INTRODUCTION: The application of plants as medicines dates back to the prehistoric period and has been a central component of health care in many cultures for centuries, dating as far back as 5,000 years [1].

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Medicinal plants have curative properties due to the presence of various complex chemical substances of different compositions, which are found as secondary plant metabolites in one or more parts of these plants [2].

Herbal medicines are in great demand in both developed and developing countries as a source of primary health care owing to their attributes having wide biological and medicinal activities [3]. Medicinal plant functions as an efficient antioxidant to scavenge free radicals and have greater importance as a therapeutic agent in

preventing or slowing oxidative stress-related degenerative diseases like hepatotoxity, ulcers, inflammations, nephrotoxicity [4]. Ancient literature has prescribed various herbs for the cure of urinary troubles and renal diseases, but allopathy had not provided any safe remedy in the treatment of this ailment. Hence there is a dire need to explore indigenous knowledge on sue of common medicinal plants for the treatment of renal diseases and to scientifically validate their ethno meidicinal use. Among wide varieties of medicinal plants used traditionally in the treatment of urinary troubles *Grewia tiliaefolia* is one such. Ethnomedicinal databases stated that the fruits of *Grewia tiliaefolia* had been used traditionally in the treatment of urinary problems [5]. So the present study was focused on screening the phytochemicals present and scientifically validate the ethnomedicinal use of fruits this plant in renal problems.

MATERIALS AND METHODS:

Collection of *Grewia tilifolia* fruits: Fruits of *Grewia tilifolia* were collected from Talakona hills of, Chittor dist., A.P and authenticated by Botanist Dr. K. Madhava Chetty, Asst. Professor, Dept. of Botany, S. V. University and a voucher specimen (No. 1516) was deposited in S. V. University Botany Dept., Tirupati.

Preparation of Ethanol Extract: Fruits of *Grewia tilifolia* were shade dried and powdered in a Wiley mill. The powdered fruits were defatted with petroleum ether and then macerated with ethanol for 24 h. Macerated material was subjected to hot extraction followed by distillation.

Phytochemical Analysis: Preliminary phyto chemical screening: Preliminary phytochemical screening was carried out for ethanol extract of *Grewia tilifolia* (EEGT) for the presence of active phytochemical constituents as per standard methods [6].

Thin Layer Chromatography: The ethanol extract was subjected to Thin layer chromatography using pre-coated TLC plates using Toluene: Ethyl acetate: Formic acid (6:4:0.2) as a solvent system for the detection of flavonoids.

HPTLC Analysis: HPTLC analysis was carried out in the twin through chamber 20 × 10 cm, and the solvent system used is Toluene: ethyl acetate: formic acid (6:4:0.2). The solvent front position is adjusted to 70 mm, volume flow was maintained to 10 ml, and temperature is 60, and time taken is 5 min. Detection is carried out using UV Visible spectroscopy.

HPLC Analysis: Extract is subjected to HPLC analysis. The model of HPLC is Shimadzu LC- 20 AD and the pump adopted is Binary pump, column phenomenon RP C18 (200 × 4.6 mm) 5µ is used, and the detector is PDA (Photodiode Array) with wavelength 254 nm. The mobile phase employed was methanol and water (55:45) and the flow rate maintained is 0.8 ml/min. The injection Volume is 20 uL.

GC MS Analysis: GC MS analysis was performed for EEGT. The instrument used is QP 2010 plus, and the oven temperature is maintained at 50. The injection temperature is about 2500 °C. The split mode injector is used linear velocity flow control mode is maintained. The pressure was maintained at 29.7 Kpa, and column flow was adjusted to 0.72 ml/ min, and the total flow is 7.9 ml/ min.

Pharmacological Studies: Pharmacological studies were initiated with prior permission from the IAEC (Approval no. CPCSEA /1677/ PO/ Re/s /2012/IAEC/19). An experiment was performed as per CPCSEA guidelines.

Acute Toxicity Studies: Acute toxicity studies were performed by employing OECD 423 guidelines [7].

Evaluation of Nephroprotective Activity: Nephroprotective effect of EEGT was evaluated at two different dose levels *i e*., 200 and 400 mg/kg body weight in curative and prophylactic regimens. Nephrotoxicity was induced by a single intraperitoneal (i.p.) cisplatin injection (5 mg/kg b.w.). Experimental animals were systematically randomized into nine groups of six animals each, and the following treatment schedule was employed:

Group-I: Normal control- a vehicle for 5 days.

Group-II: Cisplatin on day 1+ vehicle from day 5 to day 9.

Group-III: Cisplatin on day 1 + EEGT (200 mg/kg b. w.) from day 5 to day 9.

Group-IV: Cisplatin on day 1+ EEGT (400 mg/kg b. w.) from day 5 to day 9.

Group-V: Cisplatin on day 1+ Cystone from day 5 to day 9

Group-VI: Vehicle from day 1 to day 5 + cisplatin (5 mg/kg, i.p.) on day 5.

Group-VII: EEGT (200 mg/kg b. w.) from day 1 to day 5 + cisplatin on day 5.

Group-VIII: EEGT (400 mg/kg b. w.) from day 1to day 5 + cisplatin on day 5.

Group-IX: Cystone from day 1to day 5+ Cisplatin on day 5

Group-X: Only higher dose of EEGT (400 mg/kg b. w.) from day 1to day 5.

At the end of treatment, urine was collected with the help of metabolic cages and the urine samples were subjected for estimation of urinary functional parameters. The animals were sacrificed on the day 11 (Except Group- I & X sacrificed on day 6) by cervical decapitation and blood samples were collected by cardiac puncture and were used for estimation of serum markers.

Assessment of Nephroprotective Aactivity: Biochemical tests of kidney function were estimated by using commercial kits as per standard methods [8]. Anti-oxidant studies are carried out as per standard methods to the isolated kidney tissue [9]. Further histological studies also conducted to the renal tissue [10].

Statistical Analysis: Statistical analysis carried out using Graph Pad prism software. The data was expressed as mean + standard error. One way ANOVA and Tukey-Kramer multiple comparison tests were performed and Mean values having $p<0.05$ considered as significant.

RESULTS: Preliminary phytochemical studies: Phytochemical screening of the EEGT revealed the presence of proteins, flavonoids, tannins and phenolic compounds.

Thin Layer Chromatography: The movement of the active compound was expressed by its retention factor (R_f). Three spots (R_f values: 0.32, 0.41 and 0.64) were observed out of them R_f value of one spot is matched with that of Quercetin 0.41 **Fig. 1**.

High-Performance Thin-Layer Chromatography: HPTLC fingerprint of EEGT has been depicted in **Fig. 2**. HPTLC analysis revealed total 14 compounds and R_f values started from -0.03 to 1.05. The maximum percentage of phytoconstituent was observed as [22]. 11 for compound 1and values are represented in **Table 1**.

HPLC Analysis: Upon HPLC analysis of ethanol extract of *Grewia tiliaefoliaa* peak was observed at 12.551 retention time, which was matched with Quercetin chromatogram. Hence it can be demonstrated that EEGT contains Quercetin.

GC-MS Analysis: GC-MS analysis of EEGT revealed the presence of 80 compounds **Fig. 4**. The compounds identified with their retention time and area percentage were represented in **Table 2**.

Assessment of Nephroprotective Activity: Animals received only a higher dose of extract *i.e.*, 400 mg/kg b.w., (Group- X) did not show any alterations in biochemical estimations when compared to normal animals. The effect of EEGT on cisplatin-induced nephrotoxicity was assessed by estimating serum, urinary and antioxidant parameters have been represented in **Table 3.** and **Table 4**.

Histological studies: The histological studies of rat kidney tissues are depicted in **Fig. 5.** Kidney sections of animals received cisplatin alone showed marked degeneration of tissues evidenced by necrosis, congestion, vacuolization, glomeruli, and tubular damage. His to micrographs of kidney sections treated with extracts in both curative and prophylactic regimen showed dose-dependent regeneration of the renal tissue.

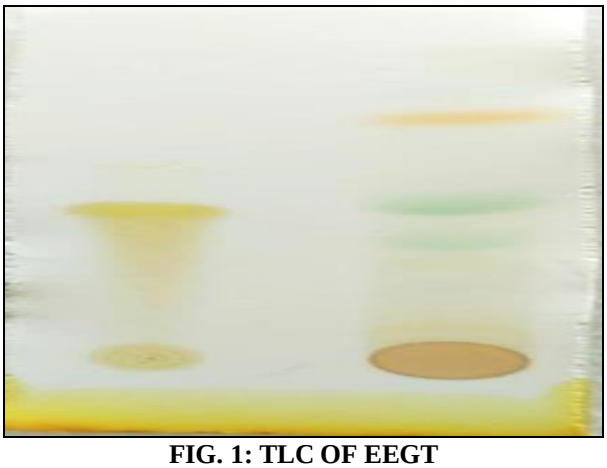

FIG. 1: TLC OF EEGT

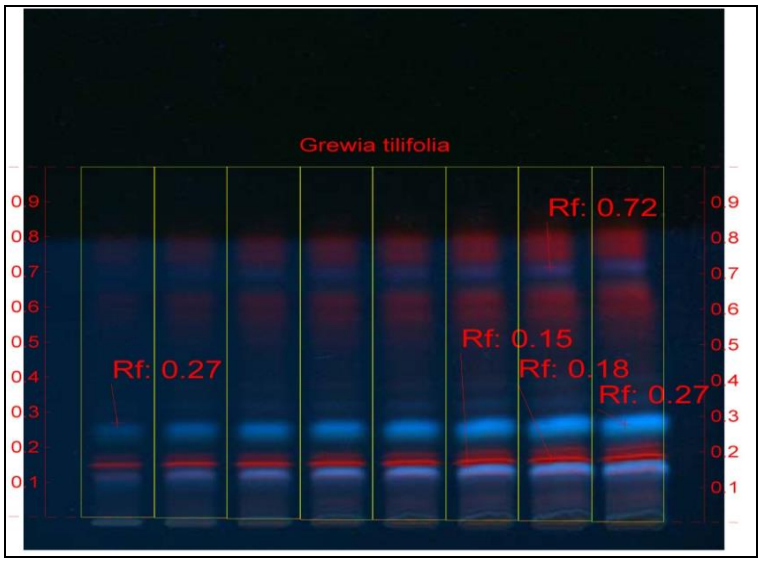

FIG. 2: HPTLC FINGER PRINT PROFILE OF EEGT

TABLE 1: HPTLC ANALYSIS OF EEGT

Peak	Start R_f	Start Height	Max Rf	Max Height	Max %	End Rf	End Height	Area	Area %
1	-0.03	2.9	0.00	611.3	22.11	0.01	571.9	5877.3	8.52
2	0.01	576.6	0.01	606.4	21.94	0.10	118.7	16254.5	23.55
3	0.12	103.2	0.16	200.4	7.25	0.17	183.4	4304.0	6.24
4	0.17	186.9	0.18	227.2	8.22	0.19	106.0	2486.4	3.60
5	0.21	105.1	0.23	124.8	4.52	0.27	75.1	3653.7	5.29
6	0.29	67.1	0.32	82.3	2.98	0.33	78.4	1922.8	2.79
7	0.38	83.4	0.42	130.1	4.71	0.45	105.2	5483.8	7.95
8	0.47	98.8	0.51	125.0	4.52	0.52	123.1	3994.7	5.79
9	0.52	123.7	0.56	142.9	5.17	0.57	139.3	4041.1	5.86
10	0.57	139.9	0.62	244.2	8.84	0.72	70.7	13918.3	20.17
11	0.73	73.8	0.76	87.0	3.15	0.77	77.6	2261.0	3.28
12	0.80	82.6	0.80	89.6	3.24	0.84	56.5	2127.9	3.08
13	0.86	54.4	0.87	67.3	2.44	0.95	30.0	2429.0	3.52
14	1.02	17.7	1.03	25.7	0.93	1.05	0.7	263.9	0.38

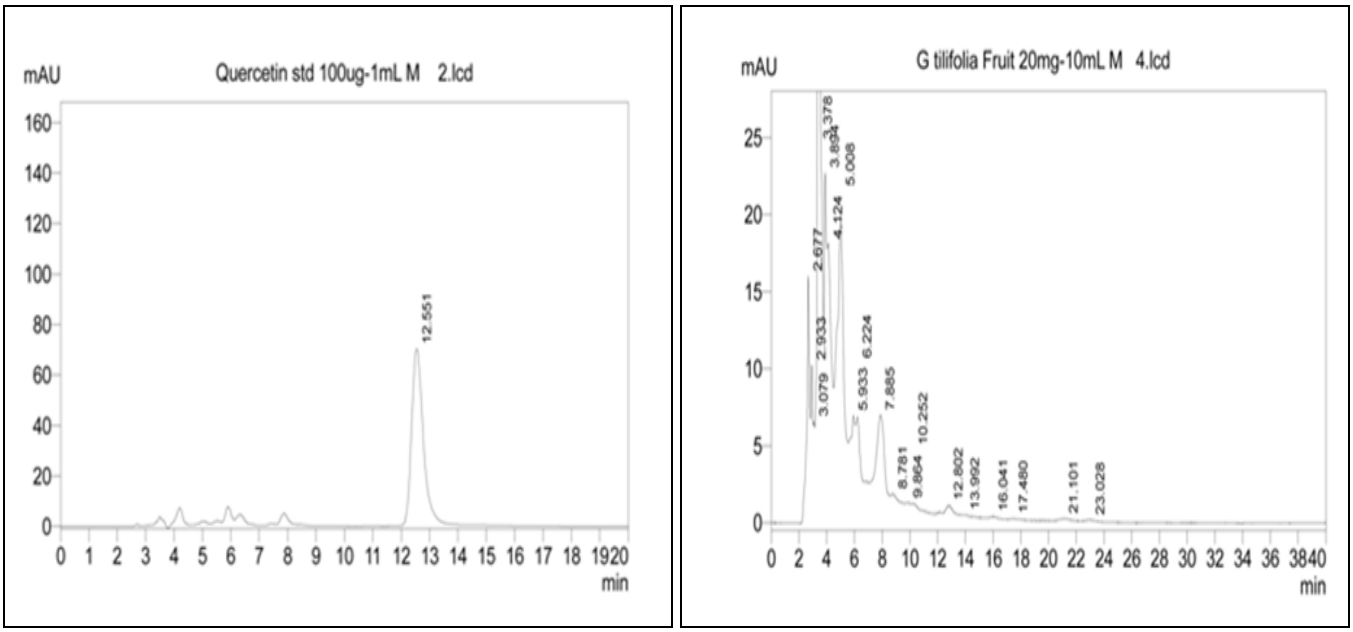

FIG. 3: HPLC ANALYSIS OF EEGT

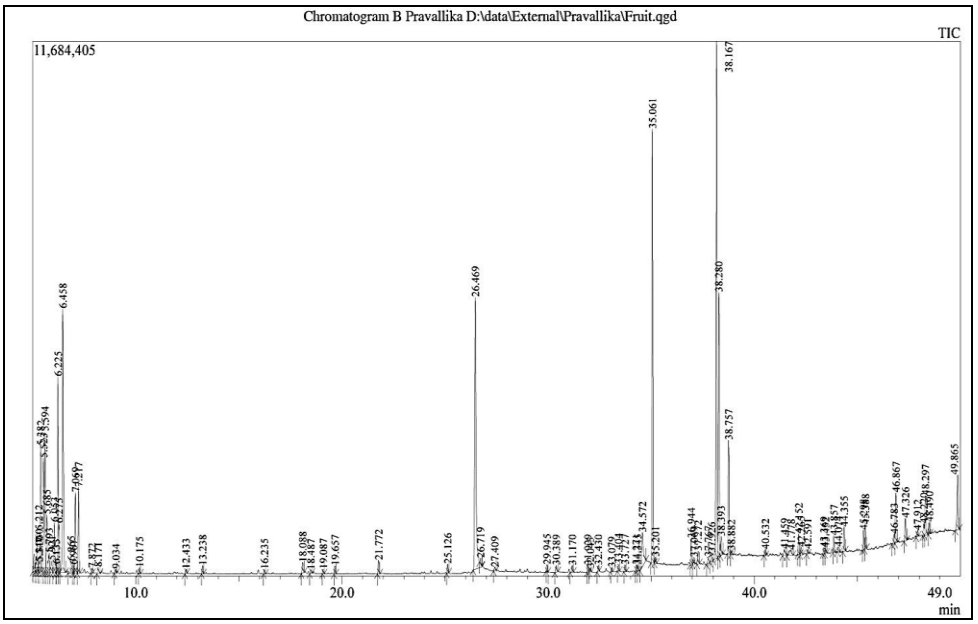

FIG. 4: GC-MS CHROMATOGRAM OF ETHANOL EXTRACT OF FRUITS OF *GREWIA TILIAEFOLIA*

TABLE 2: GC-MS ANALYSIS OF ETHANOL EXTRACT OF FRUITS OF GREWIA TILIAEFOLIA

S. no	RETENTION TIME	AERA %	Compound Name
1.	5.060	0.57	Hexane, 3-Ethyl-2-Methyl-
2.	5.147	0.24	Heptane, 2,2-Dimethyl-
3.	5.212	0.83	Heptane, 2,4-Dimethyl-
4.	5.310	0.27	Cyclopentane, 1-Ethyl-2-Methyl-, Cis-
5.	5.382	2.51	Octane, 2-Methyl-
6.	5.523	2.77	2-Ethyl-1-Hexanol
7.	5.594	3.00	Cyclohexane, Ethyl-
8.	5.685	1.40	Cyclohexane, 1,1,3-Trimethyl
9.	5.793	0.66	1-Dodecene
10.	5.921	0.42	Cyclohexane, 1,2,3-Trimethyl-, (1.Alpha)
11.	6.053	1.26	Heptane, 2,3-Dimethyl-
12.	6.133	0.18	Heptane, 4-Ethyl-
13.	6.225	4.49	Ethylbenzene
14.	6.275	0.86	Octane, 2-Methyl-
15.	6.458	8.05	Benzene, 1,2-Dimethyl
16.	6.865	0.41	Cyclopentane, 1-Methyl-2-Propyl-
17.	6.967	0.18	1-Ethyl-4-Methylcyclohexan
18.	7.069	1.99	Benzene, 1,2-Dimethyl-
19.	7.217	1.86	Nonane
20.	7.872	0.16	Cyclohexanepropanol-
21.	8.171	0.25	2-Methyloctan-1-Ol
22.	9.034	0.14	Benzene, 1-Ethyl-3-Methyl-
23.	10.175	0.13	Decane
24.	12.433	0.11	2-Furanmethanol, 5-Ethenyl
25.	13.238	0.20	Dodecane
26.	16.235	0.11	3,4,5,6-Tetramethyloctane
27.	18.088	0.35	Butanedioic Acid, Hydroxy-
28.	18.487	0.12	4-Propylbenzaldehyde
29.	19.087	0.11	Eicosane
30.	19.657	0.20	Hexadecane
31.	21.772	0.34	Hexadecane
32.	25.126	0.22	Hexadecane
33.	26.469	11.92	1,2-Benzenedicarboxylic Acid
34.	26.719	0.14	Tridecane
35.	27.409	0.12	Hydrazinecarboxamide, N,N
36.	29.945	0.18	Docosane

37.	30.389	0.25	2-(Acetylamino)-N-Ethyl-3-Ph
38.	31.170	0.18	Heptadecane
39.	31.929	0.18	2,6,10-Trimethyl,14-Ethylene
40.	32.045	0.10	2-Pentadecanone, 6,10,14-Trim
41.	32.430	0.16	Phthalic Acid, Butyl Undecyl Ester
42.	33.079	0.11	Ethyl Pentadecanoate
43.	33.404	0.18	7,9-Ditert-Butyl-1-Oxaspiro[4
44.	33.727	0.18	Hexadecanoic Acid, Methyl E
45.	34.271	0.17	Hexadecane
46.	34.345	0.19	1,2-Benzenedicarboxylic Acid
47.	34.572	1.81	Hexadecanoic Acid
48.	35.061	11.43	Hexadecanoic Acid, Ethyl Es
49.	35.201	0.17	Octadecane
50.	36.944	0.69	Heptadecanoic Acid, Ethyl Es
51.	37.069	0.21	Methyl 9-Octadecenoate
52.	37.272	0.37	2-Hexadecen-1-Ol, 3,7,11,15-Tet
53.	37.767	0.39	1,12-Tridecadiene
54.	37.926	0.65	N-Acetyl-L-Phenylalanine Ethyl Ester
55.	38.167	13.82	Linoleic Acid Ethyl Ester
56.	38.280	7.33	(E)-9-Octadecenoic Acid Ethyl Ester
57.	38.393	0.60	(E)-9-Octadecenoic Acid Ethyl Ester
58.	38.757	2.93	Octadecanoic Acid, Ethyl Est
59.	38.882	0.11	Hexadecane
60.	40.532	0.18	Hexadecanoic Acid, 1-(Hydro
61.	41.459	0.36	7-Hexadecenal, (Z)-
62.	41.778	0.44	Heneicosane, 11-Cyclopentyl
63.	42.152	0.53	Octadecanoic Acid, Ethyl Est
64.	42.265	0.27	Eicosane, 10-Methyl-
65.	42.591	0.14	9,12-Octadecadienoic Acid (Z,Z)
66.	43.369	0.17	(6e,11z)-1,6,11-Hexadecatriene
67.	43.452	0.17	Carbonic Acid, AllylPentadecyl Ester
68.	43.857	0.45	Octacosane
69.	44.074	0.22	Cyclohexane, (2-Ethyl-1-Met
70.	44.355	0.73	Di-N-Octyl Phthalate
71.	45.298	0.53	Octadecanoic Acid, Ethyl Est
72.	45.388	0.63	Heptacosane
73.	46.783	0.32	Hexadecanoic Acid, Ethyl Es
74.	46.867	1.30	Heptacosane
75.	47.326	0.71	Octacosane
76.	47.912	0.16	Hexacosane, 9-Octyl-
77.	48.220	0.34	Ethyl Tetracosanoate
78.	48.297	1.17	Hexatriacontane
79.	48.490	0.30	Squalene
80.	49.865	1.90	Heptacosane

TABLE 3: EFFECT OF EEGT ON SERUM AND URINARY PARAMETERS

Group	Treatment	BUN (mg/dl)	SC (mg/dl)	U_{TP} (mg/24h)	Cl_{cr}(ml/h/100g BWt.)
I	Normal	12.3±0.44	0.88±0.06	1.60±0.11	17.65±0.81
II	Curative control	35.46 ± 1.74^{a}	2.64 ± 0.14^{a}	8.88 ± 0.33^{a}	4.17 ± 0.34^{a}
III	Curative lower dose	22.26 ± 2.157^{b}	1.51 ± 0.17^{b}	4.46 ± 0.14^{b}	7.94 ± 1.29^{b}
IV	Curative higher dose	20.7 ± 2.90^{b}	1.46 ± 0.20^{b}	3.64 ± 2.11^{b}	14.26±.73b
V	Curative standard	19.3 ± 0.26^{b}	1.44 ± 0.01^{b}	4.90 ± 0.29^{b}	14.4 ± 0.32^{b}
VI	Prophylactic control	35.16 ± 1.39^{a}	2.5 ± 0.14^{a}	9.42 ± 0.26^{a}	5.06 ± 0.24^{a}
VII	Prophylactic lower dose	31.75 ± 2.113^{b}	1.95 ± 0.14^{c}	8.12 ± 0.23^{ns}	9.68 ± 0.72^{c}
VIII	Prophylactic higher dose	26.43 ± 2.56^{ns}	1.78 ± 0.28^{ns}	5.44 ± 0.18^{c}	12.02 ± 0.28^{c}
IX	Prophylactic standard	25.87±3.613	1.7 ± 0.20^{c}	6.63 ± 0.19^{ac}	10.13 ± 0.41^{c}
X	Only higher dose	11.4 ± 0.32^{ns}	0.88 ± 0.08^{ns}	1.67 ± 0.11^{ns}	18.72 ± 6.58^{ns}

Each value represents Mean ± SEM of 6 animals in each group. a: P 0.05 when compared to Group- I; b: P 0.05 when compared to Group-II; c: P 0.05 when compared to Group-VI and ns: not significant.

TABLE 4: EFFECT OF EEGT ON ANTIOXIDANT STUDIES

Group	Treatment	LPO (µmol/mgprotein)	GSH (µmol/mgprotein)	CAT (µmol/mgprotein)	SOD (µmol/mgprotein)
I	Normal	1.81 ± 0.23	109.54 ± 2.67	22.40 ± 0.52	22.32 ± 0.64
II	Curative control	11.50 ± 1.21[a]	66.22 ± 12.21[a]	11.62 ± 0.18[a]	11.60 ± 0.19[a]
III	Curative lower dose	10.76 ± 1.17[b]	99.22 ± 14.83[b]	17.12 ± 0.31[b]	17.11 ± 0.22[b]
IV	Curative higher dose	6.24 ± 0.28[b]	106.02±14·690b	19.18 ± 0.32[b]	19.21 ± 0.23[b]
V	Curative standard	6.26 ± 0.24[a*]	89.67 ± 2.44[ns]	18.96 ± 0.31[b]	19.04 ± 0.29[b]
VI	Prophylactic control	11.53± 1.34[c]	66.43 ± 1.06[ac]	11.59 ± 0.17[a]	9.66 ± 2.03[a]
VII	Prophylactic lower dose	10.63 ± 0.15[ns]	70.04± 12.12[ns]	12.56±0.14[ns]	17.02 ± 0.12[c]
VIII	Prophylactichigher dose	8.12 ± 1.84[c]	87.27±0.78[c]	18.91± 0.30[c]	17.54 ± 0.58[c]
IX	Prophylactic standard	6.99 ± 0.42[a*]	97.10±14.35[ns]	19.27 ± 0.29[c]	19.08 ± 0.45[c]
X	Only higher dose	1.70 ± 0.23[ns]	111.30 ± 3.25[ns]	22.43 ± 0.64[ns]	20.75 ± 0.30[a]

Each value represents Mean ± SEM of 6 animals in each group. a: P 0.05 when compared to Group- I; b: P 0.05 when compared to Group-II; c: P 0.05 when compared to Group-VI and ns: not significant.

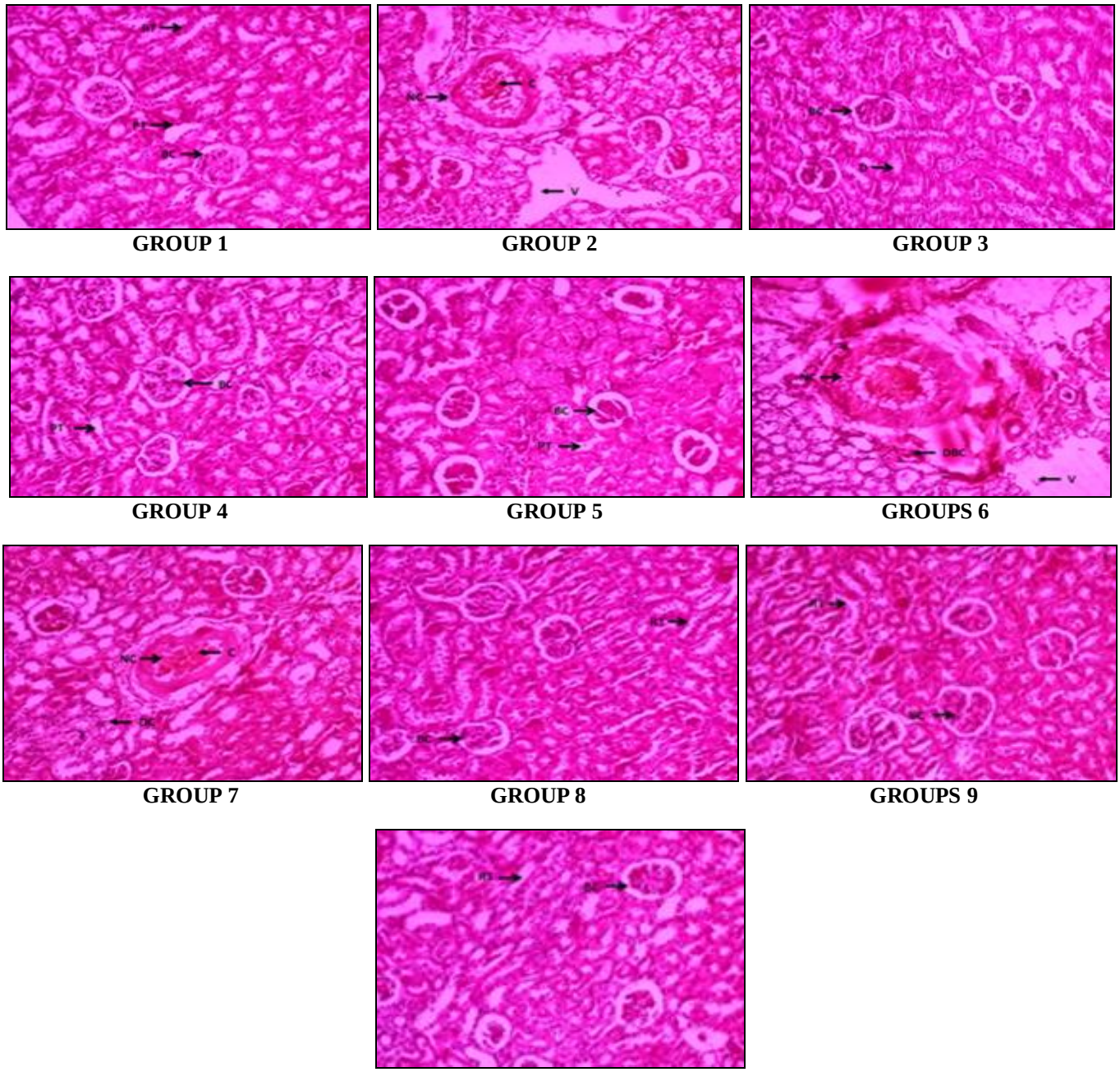

FIG. 5: HISTOMICROGRAPHS OF KIDNEY SECTIONS RT- Renal tubule; PT- Proximal tubule; BC- Bowman's capsule; DC-Degenerative changes NC- Necrosis; V- Vacuolization; C- Congestion

DISCUSSION: The kidney is the major target organ for exogenous toxicants. Nephrotoxicity induced by drug exposure is one of the most common health complications occurring in patients in critical care units [11]. For this reason, the investigation of various strategies to mitigate nephrotoxicity is an active area of research. Recently medicinal plants that exhibit strong antioxidant properties have emerged as promising candidates for the amelioration of nephrotoxicity [12]. Nephrotoxicity is a key complication in cancer patients undergoing cisplatin therapy. Cisplatin-induced nephrotoxicity is a multifaceted process and involved several mechanisms such as the formation of reactive oxygen species, inflammation and mitochondrial dysfunction [13, 15].

In our study, ethanol extract of fruits of *Grewia tilifolia* was screened for nephroprotective activity at 200 and 400 mg/kg b.w. in both curative and prophylactic regimens. Induction of nephrotoxicity by Cisplatin is assumed to be a rapid process involving reaction with proteins in the renal tubules because this renal damage occurs in the first hour after administration [16]. Hence it is essential that the protective agent should be present at an ample concentration in renal tissue before the redress. This is the reason underneath the prophylactic regimen. Cisplatin at a solitary dose of 5 mg/kg b.w. was decent to turn out nephrotoxicity. The inference of nephrotoxicity by cisplatin was manifested in this research by raise in BUN, SC, UTP and a decline in Creatinine clearance which comes in consonance with earlier reports [17]. This may come from altered glomerular filtration and an increase in reactive oxygen species. Cisplatin also declined GSH content, SOD, and CAT activities, whereas the lipid peroxidation was increased. These results were consistent with earlier reports that oxidative stress was thought to contribute to the pathogenesis of nephrotoxicity in cisplatin-treated animals [4].

However, treatment with ethanol extract of *Grewia tiliaefolia* in both curative and prophylactic regimens conversed the effect induced by cisplatin in dose-dependent passion. This may be due to the beef-up of glomerular filtration and activation of antioxidant system. This comes in correlation with earlier reports that plants with antioxidant principles such as *Nigella sativa*, *Asparagus racemosus*, *Plumeria rubra,* and *Boerhaavia diffusa* showed significant protection against cisplatin-induced nephrotoxicity [18, 21]. In the current study, preliminary phytochemical studies revealed the presence of flavonoids, tannins and other phenolic substances. Flavonoids are bioactive compounds with a myriad range of pharmacological activities like antioxidant, anti-inflammatory and anticancer activities. For example, flavonoids like rutin, quercetin, scutellarin and hesperetin exhibited significant activity against cisplatin-induced nephrotoxicity [22, 26]. Upon TLC and HPLC analysis of EEGT revealed the presence of Quercetin which strongly supports the nephroprotective activity of ethanol extract of fruits of *Grewia tilifolia*.

Further GC-MS analysis carried out for the extract revealed the presence of many bioactive phyto-constituents, which may be indirectly contributed to the pharmacological activity of these fruits. Thus the possible mechanism by which ethanol extract of fruits of *Grewia tilifolia* showed protection against cisplatin-induced nephrotoxicity may be the due presence of phytoconstituents which causes degenerative changes in the kidney.

CONCLUSION: The findings of the present study reveal the presence of a wide range of phytoconstituents from the fruits of *Grewia tilifolia,* and it effectively ameliorated cisplatin-induced nephrotoxicity in rats. Further, the present study provides corroborative scientific evidence for ethnomedicinal use of fruits of *Grewia tilifolia* in renal problems.

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CONFLICTS OF INTEREST: No conflicts of interest

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