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Clinico-Biochemical and Nephroprotective Effects of Medicinal Herbs on Gentamicin Induced Nephrotoxicity in Wistar Rats

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Abstract

Nephrotoxicity followed by kidney disease is the main complication of gentamicin treatment. Medicinal plants and herbs have played an important role in the prevention and treatment of kidney diseases. With this concern the ethanol extract of *Zingiber officinale* rhizomes, ethanol extract of *Tinospora cordifolia* roots and methanol extract of *Cajanus indicus* leaves were compared for their nephroprotective effect in the Wistar rats. A total of 48 Wistar rats were distributed into six equal groups (n=8) and were exposed to gentamicin sulphate @ 100 mg/kg orally for 7 days to induce nephrotoxicity in 5 groups. Group G1 was kept as healthy control and group G2 was considered as untreated induced nephrotoxic control, whereas the rats of groups G3, G4, G5 and G6 were given, along with gentamicin sulphate @ 100 mg/kg, extracts of *Zingiber officinale* @ 400 mg/kg b.wt, *Tinospora cordifolia* 200 mg/kg b.wt, *Cajanus indicus* @ 400 mg/kg b.wt and syrup Cystone @ 500 mg/kg b.wt., respectively, orally for 7 consecutive days as neproprotective drugs. A significant ($P \leq 0.05$) increase was observed in the values of plasma BUN, creatinine, urea, ALP, GGT, uric acid, calcium and phosphorus, whereas the total protein and albumin were found significantly ($P \leq 0.05$) decreased on day 7 in rats receiving gentamicin alone (G2). However, there was no significant alteration in the values of above mentioned parameters in rats of G1 (healthy control), G4 and G6, which remained within the normal physiological range, suggesting nephroprotective role of herbal extracts in rats.

Key words: Gentamicin, Nephrotoxicity, *Zingiber officinale*, *Tinospora cordifolia*, *Cajanus indicus,* Nephroprotection.

Introduction

Kidneys are affected by several environmental agents mainly comprising toxic chemicals and synthetic drugs. Among the various nephrotoxic agents, aminoglycosides have long been recognized as the commonest causes of drug-induced nephrotoxicity (Walker and Duggin, 1988). Gentamicin (100 mg/kg/day) when administered for 7 days produced nephrotoxicity characterized by rising in serum creatinine and blood urea nitrogen levels and decreasing glomerular filtration rate and renal blood flow (Sadeghi *et al.,* 2015).

Management of nephropathies appears to be difficult task if it is in advanced stage of renal failure. Several reports have shown that medicinal herbs can improve the activities of antioxidant enzymes (Valipour *et al.,* 2016) and are known for their nephroprotective effects. Many researchers have found the nephroprotective action of *Zingiber officinale* (Rodrigue*s et al.,* 2014), *Cajanus indicus* (Sarkar *et al.,* 2006) and *Tinospora cordifolia* (Chavan *et al*., 2016) by mitigating renal oxidative stress and inflammation under different drug induced nephrotoxicity model. Pre-treatment with Cystone (5 ml/kg, PO) for 7 days, alleviated the glycerol induced renal dysfunction significantly by maintaining serum urea, creatinine, BUN and kidney weight to body weight ratio near to normal range, and also improved the creatinine clearance compared to untreated positive control (Rafiq *et al.,* 2012). The object of this study was to examine comparative clinico-biochemistry and nephroprotective effects of three medicinal herbs *Zingiber officinale, Cajanus indicus* and *Tinospora cordifolia* on gentamicin induced nephrotoxicity in Wistar rats.

Materials and Methods

A total of 48 healthy adult Wistar albino male rats, weighing approximately 250-300 gram were procured from the authorised supplier after approval from Institutional Animal Ethics Committee. The rats were housed in cages and acclimatized for 5 days in the small animal house of the college before initiating the experiment. During the course of the experiment, rats were provided with standard laboratory animal ration and clean RO water *ad libidum.* The animals were equally distributed through randomization into six groups each containing eight rats and were subjected to different treatment as shown in Table 1

Table 1: Experimental design for comparative study of three nephroprotective herbal extracts and Cytone syrup in rats

Sr. No.	Name of Gr.	No. of rats	Treatment details
1.	G1 (HC)	08	Normal Saline i.p. for 7 consecutive days.
2.	G2 (GS)	08	GS 100 mg/ kg i.p. for 7 consecutive days.
3.	G3 (GS+EEZO)	08	GS 100 mg/ kg i.p. plus EEZO @ 400 mg/kg b. wt. PO for 7 consecutive days.
4.	G4 (GS+EETC)	08	GS 100 mg/ kg i.p. plus EETC @ 200 mg/kg b. wt. PO for 7 consecutive days.
5.	G5 (GS+MECI)	08	GS 100 mg/ kg i.p. plus MECI @ 400 mg/kg b. wt. PO for 7 consecutive days.
6.	G6 (GS+CS)	08	GS 100 mg/ kg i.p. plus syrup Cystone @ 500 mg/kg b. wt. PO for 7 consecutive days.

(HC= Healthy control, GS=Gentamicin sulphate; EEZO = Ethanol extract of Zingiber officinale rhizome, EETC = Ethanol extract of Tinospora cordifolia roots, MECI = Methanol extract of Cajanus indicus leaves, SC= Cystone syrup, a standard drug).

In order to induce nephorotoxicity, Gentamicin sulphate (Gentaject®, Provet Pharma Pvt Ltd) was given intraperitoneal (i.p.) @ 100 mg/kg b.wt as per Table 1. Syrup Cystone (Himalaya Drug Co) @ 500 mg/kg b.wt orally was used as a standard curative drug.

Preparation of Herbal Extracts

The selected herbs, i.e., *Zingiber officinale (*zinger*)* rhizomes, *Tinospora cordifolia* (guduchi) roots and *Cajanus indicus* (pigeon pea) leaves were procured from local market. The parts of test herbs were subjected to extraction and the aqueous ethanol extract of rhizome of *Zingiber officinale* (EEZO), ethanol extract of roots of *Tinospora cordifolia* (EETC) and methanol extract of *Cajanus indicus* leaves (MECI) were prepared as described by Ajith *et al. (*2007), Uppuluri *et al.* (2013) and Sarkar *et al*. (2006), respectively.

The extracts, thus obtained were stored at 4°C. The required quantity of test item (i.e. extracts) for each dose group was weighed. Test item was mixed with required volume of Tween 80 by triturating. The known volume of carboxymethyl cellulose was added in the mixture and triturated to make homogenous mixture. Dose formulations were prepared every day prior to dosing and were used within 4 hr of its preparation. The homogenous preparations were gavaged orally as per the body weight of individual rat using a tuberculin syringe fitted with a blunt 16 gauze needle so that exact amount of extract could be dispensed.

Sample Collection and Laboratory Estimations

The micro-environment, housing, watering and feeding remained same for all the experimental rats throughout the study period. The animals were examined daily for appearance of any clinical signs. Comparative nephro-ameliorative efficacy of herbal extracts and syrup Cystone was assessed on the basis of clinical signs, and plasma biochemical alterations. The body weight of the rats was recorded on day 0 and thereafter on day 7. Blood samples from individual rats were collected from retro-orbital plexus in heparinised vials on day 0, 3 and 7 for plasma biochemistry analysis. The plasma levels of BUN, creatinine, urea, ALP, GGT, uric acid, total protein, albumin, calcium and phosphorus were estimated using standard procedures and assay kits of Reactivos GPL, Barcelona, España on biochemistry analyzer. The data were analyzed statistically using SPSS software version 20.00.

Result and Discussion

Clinical Signs and Body Weight of Rats

The rats of untreated control group (G2) that received only gentamicin sulphate exhibited signs of inappetance, rough hair coat, polyuria, and polydipsia in the later part of the experiment. Rats of groups G3, G4, G5 and G6 that received gentamicin along with herbal extracts of *Zingiber officinale*, *Tinospora cordifolia, Cajanus indicus* and syrup Cystone did not reveal any clinical signs suggestive of nephrotoxicity. However, rats of G4 and G6, receiving gentamicin along with extract of *Tinospora cordifolia* roots and syrup Cystone, respectively, were more active and alert as compared to the rats of G3 and G5 receiving gentamicin along with ethanol extract of *Zingiber officinale* rhizomes and methanol extract of *Cajanus indicus* leaves. The healthy control rats (G1) remained active and alert throughout the course of experiment.

The clinical sign showed by the rats of gentamicin control groups were similar to the findings of Rashid *et al.* (2005), who injected gentamicin s/c @ 100 mg/kg for 4 days or 60 mg/kg for 2 weeks. The lack of clinical manifestation of nephrotoxicity of GS in the rats treated with all three herbal extracts indicated the protective mechanism of these extracts similar to that of standard drug Cystone. Cuiyan *et al.* (2016) also reported polydipsia at the very first day of gentamicin administration which is in agreement with present finding. Rats receiving gentamicin along with extract of *Tinospora cordifolia* root or syrup Cystone were comparatively more active and alert than those received extracts of *Z. officinale* or leaves of *Cajanus indicus.*

Rats of all the treatment groups receiving gentamicin along with different herbal extracts and syrup Cystone showed steady increase in their body weight by day 7 as compared to day 0. However, statistically, the differences were significant only in healthy control rats (G1) and those receiving GS along with root extract of *Tinospora cordifolia* (G4), but not in G3, G5 and G6. The weight of rats receiving GS alone (G2) however remained unchanged (Table 2). However, Cuiyan *et al.* (2016) observed decline in body weight and lowered feed intake in the rats given higher dose of gentamicin. In the present investigation, failure to increase body weight in rats given gentamicin may be due to inappetance. Low feed intake and metabolic disorders have also been incriminated with decrease in body weight in gentamicin nephrotoxicity (Djebli *et al.,* 2004). The initial clinical signs of dullness, depression, anorexia, polydipsia, polyuria and loss of body weight in the GS injected groups suggested their prognostic value of suspected nephrotoxicity. The weight gain was more pronounced

in rats given extract of *Tinospora cordifolia* root, which further indicated the better efficacy of this herbal extract. This was similar to increase in body weight when pomegranate flower extract was gavaged @ 25 mg/kg to ameliorate gentamicin induced nephrotoxicity by Sadeghi *et al.* (2015).

Table 2: Body weight (g) of rats of different groups under experiment

Days	Mean ± SE body weight (n=8)					
	G1	G2	G3	G4	G5	G6
0 day	314.5±9.50[a]	318.4±8.83	318.7±8.52	319.2±8.13[a]	318.7±8.36	317.0±8.59
7 day	325.1±10.68[b]	318.1±8.86	329.5±8.43	331.2±8.12[b]	328.7±8.30	329.2±8.70

Values bearing uncommon superscripts within the column vary significantly at P ≤ 0.05.

Blood Biochemical Changes

The BUN levels in group G2 given GS alone and those G3, G4, G5 and G6 received GS along with herbal extracts or syrup Cystone were found significantly (P≤0.05) elevated as compared to healthy control rats (G1) on day 7 of the experiment. The highest value (44.37 ± 1.82 mg/dl) was recorded in rats of G2 on day 7. However, BUN levels in rats of G3, G4, G5 and G6, which received ameliorative treatment along with GS were significantly (P≤0.05) lower than the rats of G2. The levels of BUN in rats of G3 and G4 remained higher as compared to the value of healthy control group (G1) on day 7. But statistically there were no significant difference in the BUN values on day 7 in rats of G4 and G6 receiving GS along with ethanol extract of *Tinospora cordifolia* roots and syrup Cystone when compared with the healthy control group (11.30 ± 0.76 mg/dl) (Table 3).

Further, significantly (P≤0.05) higher values of plasma creatinine were recorded on day 7 in rats of G2 receiving GS alone, and in G3 and G5 receiving GS along with extract of *Zingiber officinale* and *Cajanus indicus,* respectively, than the value observed in the rats of healthy (0.99 ± 0.02 mg/dl) control group (G1). Plasma creatinine in rats of G4 and G6 receiving GS along with herbal extract of *Tinospora cordifolia* roots and syrup Cystone, respectively, did not vary significantly (P≥0.05) and remained comparable with the value in healthy control group (Table 3). Nephrotoxicity induced by gentamicin is a complex phenomenon characterized by an increase in BUN, serum creatinine levels and severe proximal renal tubular necrosis followed by renal failure (Al-Majed *et al*., 2002). The reduction in glomerular filtration rate, which is indicated by the increase in serum creatinine level, would be accompanied by an increase in BUN levels when a marked renal parenchymal injury occurs (Erdem *et al*., 2000). The present findings were also in accordance with the earlier observations (Lakshmi and Sudhakar, 2010).

Significantly (P≤0.05) higher value (9.31 ± 0.017mg/dl) of plasma uric acid was found on day 7 in rats of G2 than the value (3.50 ± 0.015) recorded in healthy control group (G1). The uric acid concentration in rats of G4 did not vary significantly and remained comparable with the control value (Table 3). The significant increase in uric acid in GS treated rats was associated with renal dysfunction as GS-induced nephrotoxicity is suggested to be a complex phenomenon characterized by an increase in serum uric acid levels and severe proximal renal tubular necrosis followed by renal failure (Al-Majed *et al*., 2002). The present observation might be due to the nephrotoxic effect of gentamicin as pointed out by others (Lakshmi and Sudhakar, 2010; Pitchai *et al.,* 2017).

A gradual and significant (P<0.05) increase in plasma total protein was observed on day 7 of the experiment over previous days in the rats of G4 receiving GS along with extracts of T. cordifolia roots, while the trend was inversed in all other groups. The decline was drastic and highly significant only in G2 receiving GS alone compared to control and even other nephro-protective groups. Further, the variation in plasma protein levels was found to be significant between groups on day 3 and day 7 of treatment. On day 7, the value of total protein was lowest (P<0.01) in the rats of

G2 given GS alone, followed by G3 & G6, G1 & G5 and the highest was in G4 (Table 3). Moreover, significant (P<0.05) reduction in albumin level was found in G2 as compared to G1. The albumin levels G3, G4, G5 and G6 remained comparable to G1 throughout the course of the experiment (Table 3). Plasma albumin and total protein decreased significantly (P<0.05) in rats given gentamicin. The rats given GS showed inappetance and had impaired kidney function, which had possibly contributed to low protein and albumin concentrations. Hypoalbuminemia and hypoglycemia are reported in hepatopathy, renal failure and fasting (Kakalij *et al.,* 2014).

Plasma ALP (U/L) activities increased significantly (P≤0.05) on day 7 in untreated control rats (G2) as compared to the values observed in healthy control rats (G1). However, the mean values of ALP activity in rats of G3, G4, G5 and G6 did not vary significantly (P≤0.05) from the value (31.4 ±0.63) of healthy control group (Table 3). As compared to healthy control group, GGT (U/L) activity in the rats of G2, G3 and G5 increased significantly (P≤0.05) on day 7. However, the values for

Table 3: Blood biochemical changes in different groups of Wistar rats under experiment

Parameters	Groups (n=8)	Mean ± SE		
		0 day	3 day	7 day
Blood urea nitrogen (BUN)(mg/dl)	G 1	10.74 ± 0.81	11.03 ± 0.80^{d}	11.30 ± 0.76^{d}
	G 2	11.06 ± 0.48^{C}	27.71 ± 1.39^{aB}	44.37 ± 1.82^{aA}
	G 3	10.06 ± 0.38^{C}	18.95 ± 0.67^{bB}	25.33 ± 0.84^{bA}
	G 4	10.59 ± 0.38^{B}	11.21 ± 0.32^{dB}	13.93 ± 0.30^{dA}
	G 5	10.84 ± 0.48^{B}	13.93 ± 0.97^{cB}	19.65 ± 1.69^{cA}
	G 6	09.97 ± 0.23^{C}	11.03 ± 0.36^{dB}	13.025 ±0.27^{dA}
Creatinine (mg/dl)	G 1	1.04 ± 0.04	1.00 ± 0.03^{c}	0.99 ± 0.02^{d}
	G 2	0.97 ± 0.03^{C}	2.28 ± 0.06^{aB}	3.36 ± 0.05^{aA}
	G 3	0.98 ± 0.02^{B}	1.14 ± 0.03^{bB}	1.80 ± 0.08^{bA}
	G 4	1.00 ± 0.03^{C}	1.08 ± 0.02^{bcB}	1.22 ± 0.02^{cdA}
	G 5	1.05 ± 0.02^{B}	1.16 ± 0.01^{bB}	1.69 ± 0.04^{bA}
	G 6	1.01 ± 0.03^{A}	1.10 ± 0.02^{bcA}	1.11 ± 0.01^{cdB}
Uric acid (mg/dl)	G 1	3.48 ± 0.063^{b}	3.41± 0.012^{d}	3.50 ±0.015^{e}
	G 2	3.49 ±0.007^{bC}	6.02± 0.062^{aB}	9.31 ±0.017^{aA}
	G 3	3.71 ±0.043^{aC}	3.91± 0.072^{bB}	4.44±0.0257^{bA}
	G 4	3.55 ± 0.039^{b}	3.61 ± 0.033^{c}	3.50 ±0.039^{e}
	G 5	3.51 ±0.040^{bC}	3.73 ± 0.057^{cB}	4.03 ±0.039^{cA}
	G 6	3.52 ±0.036^{bB}	3.61 ±0.054^{cAB}	3.68 ±0.022^{dA}
Total protein (g/dl)	G 1	7.81 ±0.012^{A}	7.80 ±0.013^{aA}	7.67 ±0.038^{bB}
	G 2	7.79 ±0.029^{A}	7.14 ±0.037^{dB}	6.41 ±0.037^{eC}
	G 3	7.73 ±0.049^{A}	7.46 ±0.056^{cB}	7.09 ±0.047^{cdC}
	G 4	7.78 ±0.022^{C}	7.86 ±0.014^{aB}	7.94±0.015^{aA}
	G 5	7.75 ±0.025^{A}	7.68 ±0.029^{bA}	7.57 ±0.039^{bB}
	G 6	7.82 ±0.009^{A}	7.70 ±0.024^{bA}	7.30 ±0.062^{cB}
Albumin (g/dl)	G 1	4.22 ±0.012^{bB}	4.24 ±0.014^{cAB}	4.27 ±0.010^{cA}
	G 2	4.26 ±0.013^{aA}	4.09 ± 0.014^{eA}	3.06 ±0.043^{eB}
	G 3	4.21 ±0.009^{bC}	4.28±0.0075^{bB}	4.46 ±0.031^{aA}
	G 4	4.23±0.013^{abA}	4.18 ±0.011^{dB}	4.22 ±0.010^{cA}
	G 5	4.20 ±0.011^{bC}	4.33 ±0.012^{aB}	4.37±0.011^{bA}
	G 6	4.22 ±0.013^{bA}	4.12 ±0.019^{eB}	4.00 ±0.027^{dC}

Values bearing uncommon superscripts (small letters in column and capital in row) vary significantly (P≤0.05).

rats of G4 and G6 receiving herbal extract of *Tinospora cordifolia* roots and syrup Cystone, respectively, remained statistically similar to the control group (Table 4). The ALP and GGT activities increased significantly ($P \leq 0.05$) in plasma of rats receiving gentamicin. These increased levels of GGT and ALP might have occurred due to GS-induced oxidative stress and hepatotoxicity arising secondary to nephrotoxicity. The present findings are in agreement with Mrudula *et al*. (2005) who reported significant increase in ALP and GGT in nephritis cases. The increase of serum GGT and ALP in the present study could be due to metabolic disorders and stress leading to anorexia and secondary hepatopathy caused by gentamicin toxicity.

Table 4: Enzymatic and blood minerals changes in different groups of Wistar rats under experiment

Parameters	Groups (n=8)	Mean ± SE		
		0 day	3 day	7 day
Alkaline phosphatase ALP (U/L)	G 1	30.59 ± 0.42^{aB}	32.67 ± 0.44^{bA}	31.4 ± 0.63^{bAB}
	G 2	30.31 ± 0.42^{abC}	36.43 ± 0.50^{aB}	46.81 ± 0.99^{aA}
	G 3	29.64 ± 0.38^{abcA}	30.32 ± 0.34^{cB}	28.49 ± 0.30^{cAB}
	G 4	29.16 ± 0.26^{bcA}	29.95 ± 0.23^{cA}	28.08 ± 0.10^{cdB}
	G 5	28.52 ± 0.30^{cd}	27.87 ± 0.56^{d}	29.19 ± 0.36^{c}
	G 6	27.93 ± 0.49^{d}	26.71 ± 0.47^{d}	26.85 ± 0.26^{d}
Glutamyl transferase GGT (U/L)	G 1	27.90 ± 0.32^{bC}	29.76 ± 0.54^{dB}	31.14 ± 0.43^{dA}
	G 2	29.43 ± 0.38^{aC}	56.72 ± 0.93^{aB}	74.42 ± 1.29^{aA}
	G 3	30.22 ± 0.40^{aC}	32.63 ± 0.44^{cB}	39.06 ± 0.46^{bA}
	G 4	29.63 ± 0.22^{aB}	30.84 ± 0.29^{dA}	29.72 ± 0.26^{dB}
	G 5	30.30 ± 0.51^{aC}	38.71 ± 0.48^{bA}	34.06 ± 0.55^{cB}
	G 6	29.55 ± 0.42^{a}	30.56 ± 0.37^{d}	29.65 ± 0.29^{d}
Calcium (mg/dl)	G 1	9.81 ± 0.012^{aA}	9.79 ± 0.013^{dA}	9.68 ± 0.029^{eB}
	G 2	9.74 ± 0.028^{aC}	$11.19 \pm .052^{aB}$	$13.82 \pm .092^{aA}$
	G 3	9.54 ± 0.041^{bcC}	10.08 ± 0.047^{cB}	10.28 ± 0.044^{dA}
	G 4	9.60 ± 0.053^{bB}	9.71 ± 0.042^{dAB}	9.80 ± 0.043^{eA}
	G 5	9.59 ± 0.036^{bC}	10.31 ± 0.041^{bB}	10.83 ± 0.036^{bA}
	G 6	9.47 ± 0.026^{cC}	9.99 ± 0.033^{cB}	$10.54 \pm .036^{cA}$
Phosphorus (mg/dl)	G 1	5.48 ± 0.013^{bcB}	5.55 ± 0.017^{dA}	5.56 ± 0.019^{dA}
	G 2	5.53 ± 0.038^{abC}	7.13 ± 0.041^{aB}	9.36 ± 0.034^{aA}
	G 3	5.48 ± 0.036^{bcB}	6.05 ± 0.038^{bB}	7.39 ± 0.35^{bA}
	G 4	5.42 ± 0.032^{cB}	5.73 ± 0.041^{cA}	5.59 ± 0.41^{dA}
	G 5	5.61 ± 0.023^{aC}	6.02 ± 0.035^{bB}	6.33 ± 0.017^{cA}
	G 6	5.48 ± 0.036^{bcB}	5.79 ± 0.032^{cA}	5.62 ± 0.024^{dB}

Values bearing uncommon superscripts (small letters in column and capital in row) vary significantly ($P \leq 0.05$).

Increase ($P \leq 0.05$) in plasma calcium concentration was found on day 3 and 7 in rats of G2 as compared to G1. The calcium level in rats of G4 did not vary significantly and was comparable with the level of healthy control group (G1). The calcium level increased significantly ($P \leq 0.05$) in rats of G3, G5 and G6 in comparison to healthy control group on day 7 (Table 4). The plasma concentration of phosphorus (mg/dl) on day 7 was found to be significantly ($P \leq 0.05$) higher in rats of G2, G3 and G5 as compared to G1 and also different among themselves. The values remained statistically same in rats of G4 and G6, at par with G1 (Table 4). Higher plasma calcium and phosphorus concentrations were found in nephrotoxic rats. Attachment, binding and uptake of gentamicin in various tissues are inversely proportional to divalent cation concentration. Calcium

competes with gentamicin for anionic phospholipid membrane binding sites. Hyperphosphatemia can result from increased intestinal absorption, decreased phosphate excretion in urine or a shift in phosphate from intracellular to the extracellular compartment. Low calcium and high phosphorus values observed in the present study might be due to metabolic alterations caused by gentamicin nephrotoxicity. Lopez-Novoa *et al*. (2011) also reported hypocalcemia in aminoglycoside toxicity, while earlier investigators have documented hyperphosphatemia as a common biochemical abnormality in advanced renal failure (Chand *et al.,* 2009).

In the present study nephrotoxicity was induced in rats by gentamicin which showed the clinical signs and confirmed by elevated plasma creatinine, BUN, GGT and decreased total protein. These values were brought to normal level in the rats treated with *T. cordifolia* and standard drug Cystone which were significantly comparable to that of healthy control group. Cystone by reducing the effect of gentamicin induced nephrotoxicity proved to be a good nephroprotective drug along with its lithotriptic, diuretic, anti-lithiatic, secondary anti-microbial, demulcent and anti-inflammatory properties in UTI cases. The findings in this study regarding the efficacy of Cystone are in agreement with various drug induced nephrotoxicity studies undertaken by El-Ghiaty *et al*. (2014) and Ravindra Reddy *et al*. (2016). The anti-oxidant property of Cystone could be one of the mechanisms behind the beneficial effect observed in the present study. Accordingly there may be similar factor responsible for the nephroprotective effect of *T. cordifolia* for which detailed studies are required to know the particular phytochemical agent and its exact mode of action.

These results confirmed the development of renal structural abnormalities and nephrotoxicity in rats after 7 days of gentamicin administration. Remarkably, the afore-mentioned clinical and functional abnormalities were significantly prevented by treatment with *T. cordifolia* in nephrotoxic rats, representing the therapeutic potential of *T. cordifolia* in inhibiting the development of gentamicin induced nephrotoxicity in rats. It was concluded from the present study that the biochemical indices like BUN, creatinine, total protein, uric acid were more sensitive prognostic markers for nephrotoxicity in rats, and all the three herbal extracts showed ameliorative potential against nephrotoxicity in rats, but comparatively extract of *Tinospora cordifolia* roots was the most effective and found to be comparable with syrup Cystone.

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