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RESEARCH ARTICLE

Renoprotective Effect of *Terminalia Chebula* on Gentamicin Induced Toxicity in Rats

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ABSTRACT

An attempt was made to study the renoprotective effect of *Terminalia chebula* in a model of gentamicin induced toxicity in rats. Gentamicin was administered intraperitoneally at the dose of 80 mg/kg body weight once daily for seven days. Significant elevation of serum biochemical parameters like blood urea nitrogen (BUN), creatinine and gamma glutamyl transferase (GGT) occurred. Histopathological examination of kidney revealed acute tubular necrosis, protein inclusion and cast in the proximal tubules. Co-treatment with aqueous extract of *Terminalia chebula* significantly restored the renal hemodynamics. On histopathological evaluation, groups treated with *Terminalia chebula* showed restoration of kidney architecture towards normal. Thus the results of the present study suggest that *Terminalia Chebula* plant extract can be used as a protective agent in gentamicin induced renal toxicity.

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INTRODUCTION

Gentamicin is an aminoglycoside antibiotic that is commonly used in the treatment of life-threatening infections. Its broad-spectrum activity, chemical stability, and its rapid bactericidal action has often made it a first-line drug in a variety of clinical situations (Singenthaler *et al*., 1986, Appel, 1990). However, a high concentration of gentamicin is nephrotoxic. It has been estimated that up to 30 % of patients treated with aminoglycosides for more than seven days showed some signs of nephrotoxicity (Mathew, 1992).. Although the pathophysiology of gentamicin induced nephrotoxicity is multi-factorial, generation of oxygen-free radicals may be a major factor in its production (Ali, 1995; Garg *et al.,* 1996). However, there is no unanimity in the literature regarding the possible mechanism(s) of toxicity, or the factors that can modulate the nephrotoxicity (Appel, 1990; Garg *et al.,* 1996). The value of aminoglycosides, including gentamicin, in clinical practice would be greatly enhanced if some means could be found to protect the kidney from this undesirable side effect. . To maintain the clinical utility of this important group of compounds, various authors have attempted co-treatment with some plant extracts which might ameliorate gentamicin induced toxicity. Recently some medicinal plants with anti-oxidant properties like garlic (Pedraza-Chaverri *et al.,* 2000), *Solanum nigrum* (Prashanthkumar *et al.,* 2000), *Rhazya stricta* (Ali, 2002), curcumin (Farombi and Ekor, 2006) and *Ginkgo bilioba* (Welt *et al.,* 2007) have been shown to protect rats against gentamicin induced toxicity. A potential therapeutic approach to ameliorate, protect or reverse gentamicin induced renal damage would have very important clinical consequences (Ali, 1995; Garg *et al.,* 1996). In the present study we have focused on the alleviatory effect of *Terminalia chebula* on the renal damage induced by gentamicin. Renal hemodynamic parameters like BUN, creatinine and GGT were monitored to study the renal damage and to understand the possible protective effects of *Terminalia chebula*.

MATERIALS AND METHODS

Inbred male albino rats of wistar strain weighing 120-150 g were obtained from Laboratory Animal Medicine, Tamil Nadu Veterinary and Animal Sciences University, Madhavaram Milk Colony, Chennai – 600 051. Animals were housed in cages and acclimatized to the standard laboratory conditions and were fed with standard dry pellet and provided drinking water *ad libitum*. This study was approved by the Institutional Animal Ethics Committee (IAEC), Madras Veterinary College, Chennai -600 007, India.

Terminalia chebula (aqueous extract) obtained from M/s Natural Remedies, Bangalore, India, silymarin obtained from M/s Microlabs, Goa, India and gentamicin

Control	Negative control
Gentamicin	Gentamicin sulphate 80 mg/kg b.wt. i/p
TC 125	Gentamicin sulphate 80 mg/kg b.wt. i/p +*Terminalia chebula* 125 mg/kg b.wt. p/o
TC250	Gentamicin sulphate 80 mg/kg b.wt. i/p +*Terminalia chebula* 250 mg/kg b.wt. p/o
Silymarin	Gentamicin sulphate 80 mg/kg b.wt. i/p + silymarin 50 mg/kg b.wt. p/o.

sulphate received from M/s Intas Pharmaceuticals, Matoda, Gujarat, India *as gratis* were used in the study. All other chemical reagents used in this study were of analytical grade

Thirty male rats were divided randomly into five groups of six in each and subjected to the following treatments.

Drug treatment was continued for seven days. At the end of the experiment, blood samples were collected from all the rats and sacrificed. Serum was separated by centrifuging at 800 g for five minutes for biochemical estimations which included blood urea nitrogen (BUN) (Murray, R.L .1984), creatinine (Murray, R.L. 1984) and gamma glutamyl transferase (GGT) (Szasz, 1969). Silymarin treated group acted as positive standard drug control.

Results were analyzed statistically by complete randomized design using SPSS software (Version 10) and comparison of the means was done by using Duncan's Post-Hoc test (multiple comparison test)

RESULTS

Renoprotective activity of *Terminalia chebula* in gentamicin induced toxicity model was tested at two different dose levels *viz*., 125 and 250 mg/kg body weight. Serum biochemical parameters were studied to assess the renoprotective effects. The mean ±S.E values of BUN, creatinine and GGT are furnished in Table 1.

BUN content of gentamicin group was found to be 79.48 ± 8.04 which was significantly (P<0.05) increased when compared with control (40.03 ± 3.58). The extract of *Terminalia chebula* at both the doses significantly (P<0.05) decreased the level of BUN content in a dose dependent manner (42.55 ± 2.06 and 38.75 ± 1.81 respectively) which was comparable to silymarin (41.54 ± 1.76) (Table 1).

There was a significant (P<0.05) increase in serum creatinine level in rats belonging to gentamicin group (1.36 ± 0.15) compared to control (0.64 ± 0.01). *Terminalia chebula* at both the dose levels were shown to significantly (P<0.05) decrease serum creatinine levels (0.73±0.02 and 0.71±0.03 respectively) which is more or less towards the control level (0.64 ± 0.01). However there was no significant difference between low and high dose groups of *Terminalia chebula*. Silymarin too significantly (P<0.05) reduced the level of creatinine (0.72 ± 0.02) (Table 1).

There was a significant (P<0.05) increase in GGT level in gentamicin group (5.51 ± 0.13) when compared to control group (4.21 ± 0.17). The extract of *Terminalia chebula* at the dose of 125 mg/kg body weight and 250 mg/kg body weight significantly (P<0.05) reduced the GGT levels to 4.74±0.16 and 4.47±0.17 respectively. Silymarin also was able to significantly (P<0.05) reduce the GGT level (4.81±0.19) towards control group when compared to gentamicin treated group. (Table 1).

Table 1: Effect of *Terminalia chebula* extract on renal biochemical parameters in experimentally induced gentamicin toxicity

Group	BUN (mg/L)	CREATININE (mg/L)	GGT (U/mg)
Control	40.03^{a}±3.58	0.64^{a}±0.01	4.21^{a}±0.17
Gentamicin	79.48^{b}±8.04	1.36^{b}±0.15	5.51^{b}±0.13
TC 125	42.55^{a}±2.06	0.73^{a}±0.02	4.74^{a}±0.16
TC 250	38.75^{a}±1.81	0.71^{a}±0.03	4.47^{a}±0.17
Silymarin	41.54^{a}±1.76	0.72^{a}±0.02	4.81^{a}±0.19

Means bearing different superscripts in the same column differ significantly (p<0.05); All values are expressed as Mean ± S.E, n=6

DISCUSSION

Appel and Neu (1977) reported that all aminoglycosides have the potential to produce reversible and irreversible renal toxicity This toxicity is due to apparent marked accumulation and avid retention of aminoglycosides in proximal tubular cells (Aronoff *et al*., 1983). The initial damage at this site is manifested by excretion of enzyme at renal tubular brush border (Patel *et al*., 1975). After several days treatment with aminoglycosides there is defect in renal concentrating ability, mild proteinuria and appearance of hyaline and granular casts. The glomerular filtration rate is reduced after additional days. The most common significant finding is a rise in plasma creatinine level. Kacew and Bergeron (1990) demonstrated that the accumulation of the drug in specific target organelles in the renal cortex may be the critical step in nephrotoxicity and it is generally agreed that gentamicin produces dose-dependent proximal renal tubular necrosis, which can be dissociated from intracellular accumulation (Bennett, 1989). Papanikolaou *et al*. (1992) reported that gentamicin is incorporated and accumulated in proximal tubule lysosomes which explain the gentamicin-induced nephrotoxicity.

There are many experimental data suggesting that gentamicin may change the levels of BUN and creatinine (Parlakpinar *et al*., 2005), which are commonly used to monitor the development and extent of renal tubular damage. An increase in the BUN value reflects an accelerated rate of protein catabolism and decreased urinary excretion. In the present study, BUN level showed a two fold surge in the gentamicin group when compared to control group. These observations were in correlation with the findings of Karahan *et al*., (2005) in which they reported that administration of gentamicin at 100 mg/kg of body weight to rats induced a marked renal failure, characterized by a significant increase in plasma creatinine and urea concentrations. *Terminalia chebula* treated group at both the dose levels and silymarin treated group showed significant decrease in BUN level when compared to gentamicin group. Ali, (2002) also found that administration of *Rhazya stricta* Decne successfully reduced the level of BUN and thereby potentially ameliorate gentamicin nephrotoxicity in rats.

The results of this study confirmed that gentamicin at a dose of 80 mg/kg/day produces nephrotoxicity, as evidenced by the reduction in glomerular filtration rate which is indicated by increase in serum creatinine. This impairment in glomerular function was accompanied by an increase in BUN. Increase in serum creatinine concentration is more significant than the increase in the BUN level in the earlier phases of kidney disease, whereas BUN begins to rise only after marked renal parenchymal injury occurs (Erdem *et al*., 2000).

In the present study, there was a two fold increase in creatinine levels also in the gentamicin group when compared to control group. This is in agreement with the results of Erdem *et al*. (2000) who reported that administration of gentamicin at 100 mg/kg body weight for eight days to female wistar rats has produced marked nephrotoxicity with significant a increase in BUN and creatinine.

Terminalia chebulae extract at both the doses were able to cause a significant reduction in creatinine level. Ali (2002) too found that administration of *Rhazya stricta Decne* could successfully reduce the level of creatinine induced by gentamicin nephrotoxicity in male wistar rats. Silymarin was also found to reduce the levels of creatinine similar to the plant extracts used in the study.

The enzyme GGT is found in higher concentrations in renal convoluted tubular brush border epithelium and is a good marker for renal tubular damage (Williams *et al*., 1981). In the present study, an elevated level of kidney GGT is indicative of renal tubular damage as induced by gentamicin group which differed significantly from control group. The results of the study were in concordance with the findings of Williams *et al*. (1981) who had observed increased levels of GGT in cortical homogenate after acute exposure to gentamicin at 100 mg/kg body weight in rats.

Terminalia chebula extract at both the dose levels used in this study and silymarin were able to cause a significant reduction in GGT level indicating the revival of tubular epithelium. Williams *et al*., (1981) also reported similar findings wherein treatment with curcumin at 200 mg/kg for two weeks significantly reduced the excretion of urinary GGT in gentamicin treated animals.

Conclusion

Renoprotective effect of *Terminalia chebula* were studied in a model of gentamicin induced toxicity in rats. Gentamicin was administered intraperitoneally at the dose of 80 mg/kg body weight once daily for seven days. Significant elevation of serum biochemical parameters like BUN, creatinine and GGT occurred. Co-treatment with aqueous extract of *Terminalia chebula* significantly restored the renal hemodynamics. Thus the results of the present study suggest that *Terminalia chebula* plant extract can be used as protective agent in gentamicin induced nephrotoxicity.

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