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Original article

Comparative Evaluation of Green Tea Pretreatment on Serum Biochemical Markers in Gentamicin-Induced Nephrotoxicity among Long Evans Rats

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Abstract

Background:
Aminoglycoside antibiotic gentamicin is a widely used clinical agent with nephrotoxicity that is dose related. The pathogenesis of kidney injury that occurs due to drugs is based on oxidative stress.

Objective:

Methods:
The experimental in vivo study was carried out from 1st July 2019 to 30th June 2020 in Sir Salimullah Medical College, Dhakawhere 30 healthy male Long Evans rats aged between 90-120 days. Statistical analysis was done using SPSS v22 with ANOVA and post hoc Bonferonni test ($p \leq 0.05$).

Results:
Green tea pretreatment significantly reduced the gentamicin-induced increases in serum creatinine (1.02±0.12 vs 1.54±0.16 mg/dL, $p<0.001$), serum urea(46.2±4.9 vs 72.3±6.1mg/dL, $p<0.001$), and BUN (22.1±2.4 vs 33.7±3.1mg. The pretreatment group had an intermediate weight of the kidneys (1.14-0.20g) compared to the control group and the gentamicin-treated group.

Conclusion:
The green tea extract is effective in providing meaningful nephroprotective effects in gentamicin-induced kidney injury, which is probably due to antioxidant effect.

Keywords: Green tea extract, Gentamicin, Nephrotoxicity, Nephroprotection

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Introduction:

The life-saving agents worldwide to rescue patients with life-threatening gram-negative bacterial infections are amino glycoside antibiotics, such as gentamicin and they have surfaced to be active against a wide range of microorganisms.[1] Gentamicin is a routine in intensive care of life-threatening infections like sepsis, peritonitis, respiratory and urinary tract infections, as it has a wide-range of antimicrobial activity and bactericidal effects. Although it is highly effective, therapeutic gentamicin is highly restricted due to its nephrotoxicity which remains a serious issue in clinical practice.[2] Nephrotoxicity has been observed in 10–25% of patients who have received gentamicin, depending on dose, duration of exposure, and inbuilt susceptibility, making it one of the biggest clinical challenges to antimicrobial therapy.[2] Gentamicin nephrotoxicity is reversible, dose-dependent acute renal damage manifested by hyperserotonemia, rising blood urea nitrogen (BUN), and decreasing glomerular filtration rate.[3] The underlying pathophysiological mechanism is largely the selective intracellular accumulation of gentamicin in kidney proximal tubular epithelial cells. This accumulation triggers an imbalance in ROS formation and removal, thus triggering the pathways of oxidative stress towards lipid peroxidation, mitochondrial injury, and apoptosis of tubular cells of the kidney.[2] Oxidative stress, therefore, becomes critical in the pathogenesis of drug-induced renal injury, and it is a most significant imbalance between ROS formation and antioxidant body defense mechanisms.[4] Lipid peroxidation in renal tissues induced by gentamicin leads to cellular membrane integrity disruption, destabilization of mitochondrial and endoplasmic reticulum structure, and ultimately tubular necrosis and functional decline.[5] At present, clinical treatment for gentamicin-induced nephrotoxicity remains inadequate, primarily involving reduction or withdrawal after the onset of renal impairment. Regrettably, as of today, there are no pharmacologic products, which can be proven to prevent or reverse the renal toxicity of aminoglycoside therapy.[3] This highlights the necessity of new strategies especially those that apply natural products with antioxidant and cytoprotective properties. Natural antioxidants have become a subject of an increased interest in the recent past due to the emergence of novel methods of treatment against oxidative stress-induced tissue damage. Among them, there is green tea, a ubiquitous extract of Camellia sinensis, which is full of polyphenolic compounds, such as epigallocatechin gallate (EGCG) and catechin and epicatechin, which have a strong radical scavenging and antioxidant properties.[6] These bioactive compounds are found to inhibit oxidative stress in liver, heart, and nervous system and in chemical induced organ toxicities.[7,8] This has been notwithstanding the lack of experimental studies that specifically describe the nephroprotective effects of pre-treating animals with gentamicin induced renal injury with green tea.[9] The present study, therefore, sought to discuss the protective effects of green tea extract pretreatment in gentamicin induced nephrotoxicity by estimating the serum renal function markers and relating these biochemical changes with the histopathological changes. The pretreatment treatment with green tea must lower the increase in the serum creatinine, urea, and BUN levels caused by gentamicin by a significant margin due to its strong antioxidant and membrane-stabilizing effects. The identification and clarification of the green tea protective mechanisms shall be used to come up with supportive adjuvant treatment strategies to prevent or reduce drug-induced renal injury in the clinic.

Methods:

The experimental in vivo study was carried out from 1st July 2019 to 30th June 2020 in the Department of Physiology, Sir Salimullah Medical College, Dhaka, with the help of an ethical clearance of the Institutional Ethics Committee (IEC). Purposive sampling was used to select 30 healthy Long Evans male rats between the age of 90 to 120 days and 150-200 g, after which they were randomized. The sample size was determined according to the level of serum creatinine in the study and control groups and it was estimated to 10 rats/group. The rats were all acclimatized for 14 days of standard conditions (23±2 C, 12-hour light-dark cycle) with access to food and water in a free environment. The animals were then put into control (Group A) and experimental (Group B) groups. Group A was a baseline control (A1) that was treated with saline and a gentamicin-treated control (A2) that was administered 80 mg/kg/day intraperitoneally in the final three days. Group B was administered with extract of green tea (300mg/kg/day orally over 28 days) and on the final three days, gentamicin was injected. The feasibility of the study was a pilot study aimed at establishing the most effective dose of gentamicin as a nephrotoxic. At the end of the research, rats were sacrificed and kidney and blood sampled. Kidney tissue was also evaluated to determine the content of MDA and histopathological changes, and the measurements of serum creatinine, urea and BUN were performed using automated analyzers. Preparation of histology slides and visualization under a microscope were carried out and photomicrographs obtained. The SPSS v22 was used to run statistics and the results reported as mean±SD. Where applicable, ANOVA with post hoc Bonferonni, paired t-test and Fisher exactly test were used with $p \leq 0.05$ being the criterion of statistical significance.

Results:

The text describes a study on three groups of rats: Group A1 (baseline control), Group A2 (gentamicin control), and Group B (gentamicin and green tea). The groups were similar in age and body weight, confirming randomization. There were no differences in body weight changes ($p=0.07$), but kidney weight varied significantly ($p<0.001$), with Group A2 showing the highest weight at 1.32 g, followed by Group B at 1.14 g,

Table-I: Baseline characteristics of study population (N=30)

Baseline characteristics	A1 (Baseline Control)	A2 (Gentamicin Control)	B (Green Tea + Gentamicin)	p-value
Number of rats	10	10	10	-
Age (days, mean±SD)	104±8	106±7	105±6	0.72
Initial body wt (g)	175.8±9.8	182.0±13.2	179.1±7.8	0.43
Final body wt (g)	212.3±7.4	211.8±9.2	220.2±9.1	0.07
% Change in body wt	21.1±6.3	16.7±5.4	23.1±6.3	0.07
Kidney wt (g)	0.87±0.07	1.32±0.18	1.14±0.20	<0.001

Table-II: Serum renal function markers across groups

Parameter	A1 (mean±SD)	A2 (mean±SD)	B (mean±SD)	ANOVA p
Serum creatinine (mg/dL)	0.74±0.09	1.54±0.16	1.02±0.12	<0.001
Serum urea (mg/dL)	30.4±2.9	72.3±6.1	46.2±4.9	<0.001
BUN (mg/dL)	14.1±1.4	33.7±3.1	22.1±2.4	<0.001

and Group A1 at 0.87 g (Table-I).

Table-II showed important serum renal function measurements from three test samples. Serum creatinine was higher in the gentamicin-treated group (1.54±0.16 mg/dL) compared to the baseline control (0.74±0.09 mg/dL), indicating severe kidney damage (ANOVA p<0.001). Green tea pretreatment lowered creatinine to 1.02±0.12 mg/dL. Serum urea levels were also high in the gentamicin group (72.3±6.1 mg/dL) but reduced to 46.2±4.9 mg/dL with green tea (p<0.001). Blood urea nitrogen increased to 33.7±3.1 mg/dL in gentamicin-treated rats, reduced to 22.1±2.4 mg/dL with green tea pretreatment (p<0.001).

Table-III shows comparisons of renal function among different experimental groups. Significant differences were found, especially with green tea pretreatment, which affected kidney function compared to control groups (p=0.001 or p=0.002). The gentamicin-treated group had notable kidney damage. Green tea did not fully inhibit this damage but offered strong protection against gentamicin effects.

Table-III: Pairwise post-hoc (bonferroni) comparisons among groups

Parameter	A1 vs A2	A1 vs B	A2 vs B
Serum creatinine	<0.001	0.002	<0.001
Serum urea	<0.001	<0.001	<0.001
BUN	<0.001	<0.001	<0.001

Figure-2 showed the correlations among key renal function and morphological parameters in experimental rats. Good positive values were obtained between serum urea and creatinine (r=0.89), between BUN and creatinine (r=0.85), and between serum urea and BUN (r=0.91), in the fact that the two tended to increase in parallel during nephrotoxicity. Serum creatinine was moderately correlated with kidney weight (r=0.66), which supports the idea of hypertrophic alteration to accompany biochemical injury, whereas, percentage change in body weight was associated negatively (r=0.58), which supports loss of weight in more severely impaired rats.

Table-IV revealed the post-hoc comparisons involving all the renal function markers with the Bonferonni correction that is a rigorous statistical test of the differences between the experimental groups with multiple tests. The results indicate that the serum creatinine levels were not equal between all groups of pairwise comparison: baseline control group and gentamicin-treated control group (A1 vs A2, p<0.001), baseline control group and green tea-pretreated group (A1 vs B, p=0.002), as well as, there was significant difference between pretreated and gentamicin-treated group (A2 vs B, p<0.001). The patterns of serum urea and BUN levels were also similar in all three comparisons with p<0.001, i.e. highly

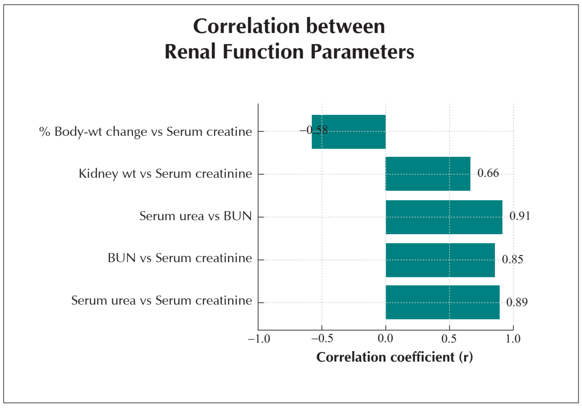
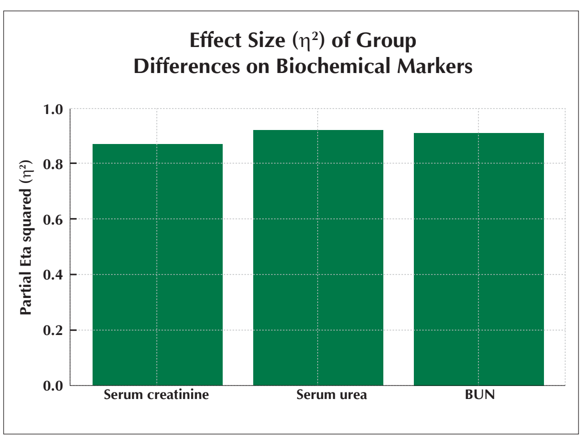


Figure-1: Correlation between renal function parameters. Good positive correlations were found between serum urea and creatinine (r=0.89), BUN and creatinine (r=0.85), and serum urea and BUN (r=0.91) during nephrotoxicity. Serum creatinine had a moderate correlation with kidney weight (r=0.66),whereas, percentage change in body weight was associated negatively (r=0.58), which supports loss of weight in more severely impaired rats.



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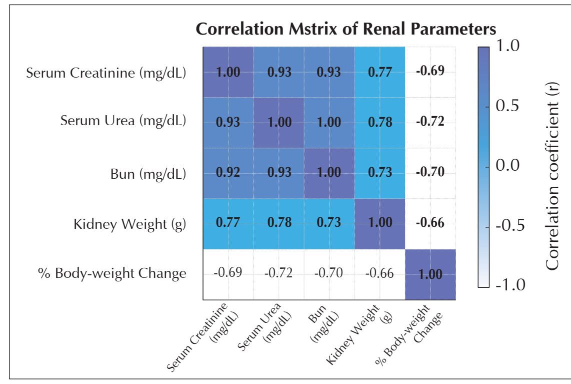

Figure-3: The correlation matrix shows relationships between renal function indices, like serum creatinine and urea, and kidney morphological parameters. It notes positive correlations with nephrotoxicity and highlights that kidney weight increases in severely injured kidneys, while body-weight change is negatively correlated with serum creatinine.

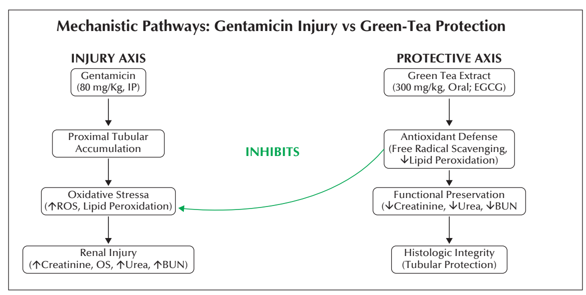

Figure-4: The text discusses how green tea helps protect against kidney damage caused by gentamicin. It notes strong positive relationships between kidney function markers (serum creatinine, urea, BUN) and kidney weight, while body-weight change showed a negative correlation with serum creatinine, indicating weight loss in more affected rats.

Table-IV: Post-hoc pairwise comparisons (bonferroni-adjusted p)

Parameter	Comparison	Bonferroni p
Serum Creatinine (mg/dL)	A1 vs A2	<0.001
	A1 vs B	0.002
	A2 vs B	<0.001
Serum Urea (mg/dL)	A1 vs A2	<0.001
	A1 vs B	<0.001
	A2 vs B	<0.001
BUN (mg/dL)	A1 vs A2	<0.001
	A1 vs B	<0.001
	A2 vs B	<0.001

significant differences in all pairwise comparisons.

Discussion:

In this article, the experiment shows that pretreatment with green tea extract significantly attenuates gentamicin-induced nephrotoxicity in rats, as indicated by the unbelievable levels of serum urea, creatinine, and BUN levels in the experimental group compared to the control group. The results confirm the previously established nephrotoxicity profile of gentamicin and expand the existing understanding of antioxidant molecules of plant origin in the prevention of kidney damage associated with drug administration.[10] The difference in serum creatinine increase in gentamicin-treated controls (1.54±0.16mg/dL) and baseline controls (0.74±0.09mg/dL) is about two times, which is directly related to the intensive impairment of glomerular filtration that is characteristic of the pathophysiology of acute kidney injury.[11] It was interesting to note that green tea pretreatment reduced serum creatinine levels by a significant value of about 34% as compared to gentamicin-treated controls indicating that polyphenolic agents induce inherent renal protective systems. The subsequent rise in serum urea and BUN in animals treated with gentamicin is indicative of a blocked glomerular filtration process and tubular injury typical of nephrotoxicity induced by aminoglycosides. The fact that high and positive correlations have been set between these biochemical indicators (r=0.89 between urea and creatinine, r=0.85 between BUN and creatinine) indicates that a combination of these lessens indicates an increase in renal damage and confirms the use of multiple indicators in assessing extensively the nephrotoxic effect.[12] The pretreatment with green tea always reduced all three biomarkers, including serum urea (72.3 mg/dl to 46.2mg/dl) and BUN (33.7mg/dl to 22.1mg/dl), and indicated comprehensive broad-spectrum protection against functional renal derangement. These biochemical advantages refer to the fact that the green tea polyphenols, specifically, epigallocatechin gallate (EGCG), are effective in combating the cases of oxidative stress cascades which are induced by accumulation of gentamicin within proximal tubular cells.[13] Morphological findings on kidney weight provide additional evidence towards nephroprotection. Controls treated with gentamicin exhibited widespread renal hypertrophy (1.32±0.18 g), a defensive reaction against tubular damage and impairment in function. Intermediate kidney weight in the green tea group (1.14±0.20 g) suggests partial preservation of normal architecture and reduced structural remodeling.[14] The presence of moderate positive correlation between kidney weight and serum creatinine (r=0.66) suggests that the biochemical damage was followed by hypertrophic changes, and partial inhibition of the latter in the pretreatment group suggests that it acted protectionally at the structural and functional levels. These are the negative relationships between the change in body weight and the serum creatinine (r=-0.58) in severely diseased animals which are the systemic effects of advanced damage to the kidney such as metabolic imbalance and impaired absorption of nutrients. The pretreatment with green tea did not alter body weight significantly, which indicates the superiority of metabolic homeostasis and low body toxicity when compared to the control.This result is consistent with Asbaghi et al, that antioxidant polyphenols of plant origin provide multi-organ protection rather than local nephroprotection.[15] The mechanistic protection is demonstrated to include direct free-radical scavenging by green tea catechins, activation of endogenous antioxidant enzymes, and stabilization of cellular membrane integrity in proximal tubular cells that are vulnerable to gentamicin-induced lipid peroxidation.[16] However, despite significant protective effects, green tea pretreatment did not normalize renal function markers to baseline levels completely. This partial protection is a reflection either of the severity of the injury induced by gentamicin at the dose used or of potential constraints to polyphenol bioavailability and renal tissue penetration.[17] Further research ought to be done on dose-response relationships, the most appropriate time of intervention, and the possibility of combination nephroprotective drug synergies. In conclusion, this paper presents a significant rationale that green tea extract is an effective adjunctive therapy that could be used in preventing drug-induced nephrotoxicity and should be subject to further translational research in order to be applied in clinical practice in patients who need aminoglycoside therapy.

Limitations:

The study used only Long Evans rats, which may not apply to human kidney toxicity. Green tea extract's optimal dose and duration are unclear.

Conclusion:

Pretreatment with green tea extract prevents gentamicin nephrotoxicity significantly with respect to its better antioxidant effects of reducing serum creatinine, urea, and BUN by approximately 34, 36, and 34 percent, respectively, when compared to the untreated gentamicin-treated rats. The study examines how certain plant compounds, particularly polyphenols from green tea, can protect against kidney damage caused by gentamicin, an antibiotic. It found that pre-treatment with these compounds helps restore kidney function and reduces damage. The results suggest these compounds could be useful in preventing renal injury from nephrotoxic drugs. Future research will explore the best dosage and timing for green tea use and test these effects in other animal models to confirm their protective benefits.

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