Oxidative Stress and Antioxidant Response in Gentamicin-Treated Rats – Role of Green Tea Extract on Renal Malondialdehyde (MDA) Levels

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ARTICLE INFO

Received: 9 Mar 2026
Accepted: 11 Mar 2026
Published Online: 17 Mar 2026

DOI: 10.5281/zenodo.19321381

Volume: 9, Number: 1, Page: 201-206

e-ISSN: 2789-5912
ISSN: 2617-0817

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ABSTRACT

Background: Gentamicin is an effective aminoglycoside antibiotic, but its use is limited by nephrotoxicity caused by oxidative stress. Malondialdehyde (MDA) reflects oxidative damage, while enzymes like SOD, CAT, GPx, and GSH indicate antioxidant status. Green tea extract (GTE), rich in epigallocatechin-3-gallate (EGCG), possesses potent antioxidant properties that may protect against such injury. This study evaluates the protective effect of GTE on renal oxidative stress by measuring MDA and antioxidant enzyme activity in gentamicin-treated rats. **Methods & Materials:** This experimental study was conducted in the Department of Physiology, Sir Salimullah Medical College, Dhaka (July 2019–June 2020) on 30 healthy male Long Evans rats (90–120 days old, 150–200 g). Renal oxidative stress markers (MDA) and antioxidant enzymes (SOD, CAT, GPx, GSH) were measured by spectrophotometric methods, while serum creatinine, urea, and BUN were assessed using enzymatic colorimetric assays. Kidney tissues were examined histologically after H&E staining. Data were analyzed using SPSS v26, with $p \leq 0.05$ considered statistically significant. **Results:** Most rats showed elevated oxidative stress, with over two-thirds having high MDA levels and reduced antioxidant enzyme activity. Strong negative correlations between MDA and antioxidants confirmed oxidative–antioxidant imbalance. Histological analysis revealed frequent tubular damage and congestion, indicating significant renal injury and oxidative dominance in gentamicin-treated rats. **Conclusion:** Gentamicin caused significant oxidative stress and kidney damage in rats, while green tea extract effectively reduced lipid peroxidation and restored antioxidant defenses. These results highlight the protective role of green tea polyphenols against drug-induced nephrotoxicity and suggest their potential as a safe, natural adjunct to minimize kidney injury during gentamicin therapy.

Keywords: *Gentamicin-induced nephrotoxicity, Oxidative stress, Green tea extract (Camellia sinensis), Antioxidant enzymes, and Malondialdehyde (MDA)*

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INTRODUCTION

Gentamicin is a potent aminoglycoside antibiotic widely used for the treatment of life-threatening Gram-negative bacterial infections. Despite its efficacy, gentamicin's clinical use is often limited by its nephrotoxic effects, which remain a significant cause of acute kidney injury (AKI) in hospitalized patients [1]. Drug-induced nephrotoxicity contributes to approximately 60% of AKI cases globally, with aminoglycosides accounting for a substantial proportion [2]. In developing regions, where aminoglycosides are frequently prescribed due to their low cost and broad antibacterial activity, the burden of gentamicin-associated renal injury is even higher [3]. Understanding the mechanisms of this toxicity and identifying protective strategies are crucial for minimizing renal complications while preserving therapeutic efficacy. A hallmark of gentamicin nephrotoxicity is lipid peroxidation, which compromises membrane integrity and cellular homeostasis. The byproduct malondialdehyde (MDA), formed during this process, serves as a reliable biomarker of oxidative stress [4]. Elevated renal MDA levels have been consistently observed in gentamicin-treated animals, confirming the role of oxidative damage in renal pathology [5]. The accumulation of ROS also activates inflammatory signaling pathways, including NF-κB, amplifying cytokine release and tissue injury [6]. Collectively, these events culminate in tubular necrosis, glomerular damage, and reduced renal function, characterized by increased serum creatinine and blood urea nitrogen (BUN) [7]. Under physiological conditions, oxidative radicals are neutralized by a sophisticated antioxidant defense system composed of enzymatic and non-enzymatic components. Key antioxidant enzymes include superoxide dismutase (SOD), which converts O_2^- to H_2O_2, catalase (CAT) and glutathione peroxidase (GPx), which reduce H_2O_2 to water, and reduced glutathione (GSH). This major intracellular thiol maintains redox homeostasis [8]. During gentamicin exposure, however, these antioxidant defenses are significantly impaired. Studies in rats have shown reduced renal activities of SOD, CAT, and GPx, along with depleted GSH levels, accompanied by elevated MDA concentrations [9,10]. This oxidant–antioxidant imbalance reflects a shift toward oxidative predominance, resulting in cumulative lipid and protein oxidation that exacerbates cellular injury. Given this pathophysiological background, interventions that boost antioxidant capacity or scavenge ROS directly are regarded as promising approaches for preventing gentamicin-induced renal injury. A variety of antioxidants both synthetic and natural have been evaluated for their nephroprotective effects. Vitamins C and E have shown efficacy in reducing lipid peroxidation and restoring antioxidant enzyme activity in gentamicin-treated rats [11]. Similarly, several plant-derived polyphenols and flavonoids, such as curcumin, quercetin, and naringenin, have demonstrated renoprotective potential through their free radical–scavenging and anti-inflammatory properties [12]. Among these natural agents, green tea extract (GTE) stands out due to its high content of potent polyphenols known as catechins, particularly epigallocatechin-3-gallate (EGCG), which exhibits remarkable antioxidant efficacy [4,9]. Green tea (Camellia sinensis) has long been recognized for its medicinal benefits, including its antioxidant, anti-inflammatory, and metal-chelating properties. EGCG, the most abundant catechin in green tea, exerts its antioxidant effects through multiple mechanisms: direct scavenging of ROS, inhibition of pro-oxidant enzymes, and upregulation of endogenous antioxidant defenses via activation of the nuclear factor erythroid 2 related factor 2 (Nrf2) signaling pathway [13,14]. Activation of Nrf2 enhances the expression of genes encoding antioxidant enzymes such as SOD, CAT, GPx, and heme oxygenase-1 (HO-1), thereby strengthening cellular defense against oxidative stress [8]. Experimental studies have provided substantial evidence supporting the renoprotective role of GTE and EGCG in gentamicin-induced nephrotoxicity. Study demonstrated that green tea extract significantly reduced serum creatinine and BUN levels, lowered renal MDA, and restored SOD and CAT activities in gentamicin-treated rats [15]. Another study showed that EGCG supplementation attenuated oxidative stress and inflammation in renal tissues by suppressing MAPK and NF-κB pathways [16]. The collective evidence suggests that oxidative stress plays a central role in gentamicin-induced nephrotoxicity and that antioxidant intervention, particularly using natural compounds like GTE, may mitigate this effect. Since MDA is a reliable indicator of lipid peroxidation and oxidative injury, and SOD, CAT, GPx, and GSH are essential markers of antioxidant defense, their assessment provides valuable insight into the redox state of renal tissues. Therefore, the present study aims to investigate the oxidative–antioxidant balance in gentamicin-treated rats and evaluate the protective role of green tea extract by analyzing renal MDA levels and key antioxidant enzyme activities.

METHODS & MATERIALS

This experimental study was conducted in the Department of Physiology, Sir Salimullah Medical College, Dhaka, from July 2019 to June 2020, following approval from the Institutional Ethics Committee. Thirty apparently healthy Long Evans male rats aged 90–120 days and weighing 150–200g was acclimatized for 14 days under standard laboratory conditions (temperature 27–28°C, 12-hour light–dark cycle) with free access to food and water. All animals received ethanolic extract of green tea (*Camellia sinensis*) orally at a dose of 300 mg/kg/day for 28 consecutive days. To induce nephrotoxicity, gentamicin was administered intraperitoneally at 80 mg/kg/day during the last three days (days 26–28). On day 29, all rats were sacrificed under light anaesthesia, and blood and kidney samples were collected for biochemical and histopathological evaluation. Renal antioxidant enzyme activities (SOD, CAT, GPx, GSH) were assayed by standard spectrophotometric methods. Serum creatinine, urea, and blood urea nitrogen (BUN) levels were measured using standard enzymatic colorimetric methods. Renal malondialdehyde (MDA) concentration, a marker of lipid peroxidation, was determined by the thiobarbituric acid reactive substances (TBARS) method. One kidney from each animal was preserved in 10% neutral-buffered formalin for histopathological examination after hematoxylin and eosin (H&E) staining to evaluate tubular degeneration, interstitial congestion, and necrosis. Data were compiled, coded, and analyzed using the Statistical Package for the Social Sciences (SPSS) for Windows version 26. Quantitative variables such as serum creatinine, urea, BUN, and MDA were expressed as mean ± standard deviation (SD). Changes in continuous variables before and after green tea and gentamicin exposure were analyzed using paired *t*-tests, while inter-parameter relationships were explored using Pearson's correlation coefficients. Histopathological findings, expressed as categorical variables (presence or absence of tubular degeneration, congestion, and necrosis), were compared using Fisher's Exact test. Statistical significance was considered at $p \leq 0.05$.

RESULTS

Among the 30 rats, most were aged between 100–109 days (53.3%), while smaller proportions were aged 90–99 days (13.3%) and 110–119 days (33.4%). Regarding baseline body weight, the largest group (33.3%) weighed between 180–189 g, followed by 26.6% in the 170–179 g range. For kidney weight, nearly half of the subjects (43.3%) had kidneys weighing 1.0–1.19 g, whereas 30% had kidneys weighing ≥1.2 g and 26.7% had kidneys weighing under 1.0 g (*Table I*).

Table I
Basic Characteristics of the Study Population (*n* = 30).

Variable	Category	Frequency (n)	Percentage (%)
Age (days)	90–99	4	13.3
	100–109	16	53.3
	110–119	10	33.4
Body weight at baseline (g)	160–169	5	16.7
	170–179	8	26.6
	180–189	10	33.3
	190–199	7	23.4
Kidney weight (g)	< 1.0	8	26.7
	1.0–1.19	13	43.3
	≥ 1.2	9	30.0

About one-third of the rats (30.0%) had MDA levels within the normal range (≤ 2.0 nmol/mg protein), suggesting normal oxidative balance. A slightly higher proportion (36.7%) showed mildly elevated levels (2.01–3.0 nmol/mg protein), while 33.3% had markedly elevated levels (> 3.0 nmol/mg protein), indicating significant oxidative stress. Overall, the results suggest that more than two-thirds of the study population exhibited elevated MDA levels, reflecting a notable presence of oxidative stress among the subjects (*Table II*).

Table II
Distribution of Oxidative-Stress Biomarker (MDA) Levels.

MDA (nmol/mg protein)	Frequency (n)	Percentage (%)
Normal range (≤ 2.0)	9	30.0
Mildly elevated (2.01–3.0)	11	36.7
Markedly elevated (> 3.0)	10	33.3
Total	30	100.0

The distribution of antioxidant enzyme activity among the 30 study subjects shows a general trend toward reduced antioxidant defense. For Superoxide Dismutase (SOD), 60.0% of participants had reduced activity (≤ 8 U/mg protein), while 40.0% maintained normal levels. Similarly, Catalase (CAT) activity was reduced in 53.3% of subjects, with 46.7% showing regular activity. Glutathione Peroxidase (GPx) had the highest proportion of reduced activity (63.3%), compared to only 36.7% with normal levels. Lastly, Reduced Glutathione (GSH) was below normal in 56.7% of individuals (*Table III*).

Table III
Distribution of Antioxidant Enzyme Activity in the Study Population.

Enzyme	Category	Frequency (n)	Percentage (%)
Superoxide Dismutase (SOD)	Normal (> 8 U/mg protein)	12	40.0
	Reduced (≤ 8 U/mg protein)	18	60.0
Catalase (CAT)	Normal (> 45 U/mg protein)	14	46.7
	Reduced (≤ 45 U/mg protein)	16	53.3
Glutathione Peroxidase (GPx)	Normal (> 10 U/mg protein)	11	36.7
	Reduced (≤ 10 U/mg protein)	19	63.3
Reduced Glutathione (GSH)	Normal (> 5 µmol/mg protein)	13	43.3
	Reduced (≤ 5 µmol/mg protein)	17	56.7

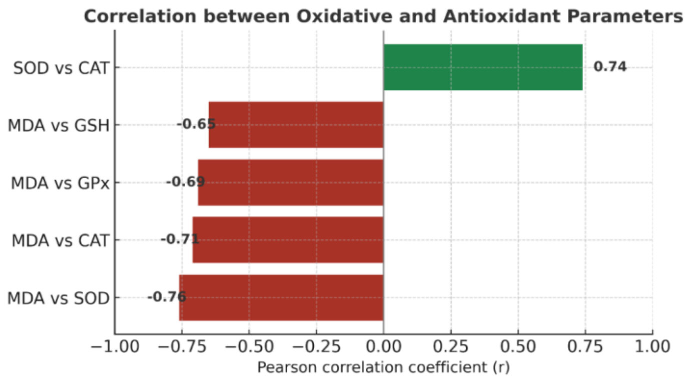

Figure I Correlation between Oxidative and Antioxidant Parameters in Experimental Rats.

Figure 1 illustrates the relationship between oxidative stress marker malondialdehyde (MDA) and key antioxidant enzymes superoxide dismutase (SOD), catalase (CAT), glutathione peroxidase (GPx), and reduced glutathione (GSH) in the renal tissue of experimental rats. Strong negative correlations were observed between MDA and all antioxidant enzymes (r = −0.65 to −0.76), indicating that higher lipid peroxidation corresponds to diminished antioxidant activity. Conversely, a positive correlation between SOD and CAT (r = +0.74) reflects coordinated enzymatic defense against reactive oxygen species. These findings confirm that oxidative stress is inversely linked with antioxidant defense mechanisms, supporting the protective role of green-tea polyphenols in mitigating gentamicin-induced nephrotoxicity.

The histopathological examination of renal tissues revealed varying degrees of structural alterations among the 30 study subjects. The most frequent abnormality was tubular epithelial degeneration, observed in 66.7% of cases, indicating widespread cellular damage in the renal tubules. Interstitial congestion was also common, affecting 56.7% of the subjects, suggesting vascular disturbances or inflammation. Hyaline casts were present in 46.7% of kidneys, reflecting protein leakage or tubular obstruction. Less frequent findings included glomerular shrinkage (30.0%) and severe tubular necrosis (20.0%), both indicative of more advanced or severe kidney injury (*Table IV*).

Table IV
Distribution of Histopathological Renal Findings (*n* = 30).

Finding	Presence n (%)	Absence n (%)	Total n (%)
Tubular epithelial degeneration	20 (66.7)	10 (33.3)	30 (100)
Interstitial congestion	17 (56.7)	13 (43.3)	30 (100)
Hyaline casts	14 (46.7)	16 (53.3)	30 (100)
Glomerular shrinkage	9 (30.0)	21 (70.0)	30 (100)
Tubular necrosis (severe)	6 (20.0)	24 (80.0)	30 (100)

The mean MDA level (2.77 ± 1.04 nmol/mg) exceeded the normal range (< 2.0), with only 30% of subjects within normal limits. A positive oxidative stress Z-score of +1.49 indicates elevated lipid peroxidation. In contrast, all antioxidant enzymes showed mean values below their respective normal thresholds: SOD (7.6 ± 2.1 U/mg; 40.0% normal, Z = −0.62), CAT (43.8 ± 8.4 U/mg; 46.7% normal, Z = −0.35), GPx (9.2 ± 2.8 U/mg; 36.7% normal, Z = −0.58), and GSH (4.8 ± 1.4 µmol/mg; 43.3% normal, Z = −0.42). The composite OABI value of −1.48 further indicates a shift toward oxidative predominance, suggesting that the antioxidant defense system was insufficient to counteract oxidative stress in most subjects (*Table V*).

Table V
Oxidative-Antioxidant Balance Index (OABI).

Parameter	Mean ± SD	Reference Range	Within Normal Range (%)	Oxidative Stress Index (Z-score)
Malondialdehyde (MDA, nmol/mg)	2.77 ± 1.04	< 2.0	30.0%	+1.49
Superoxide Dismutase (SOD, U/mg)	7.6 ± 2.1	> 8.0	40.0%	−0.62
Catalase (CAT, U/mg)	43.8 ± 8.4	> 45.0	46.7%	−0.35
Glutathione Peroxidase (GPx, U/mg)	9.2 ± 2.8	> 10.0	36.7%	−0.58
Reduced Glutathione (GSH, µmol/mg)	4.8 ± 1.4	> 5.0	43.3%	−0.42
Composite OABI	-	-	-	−1.48

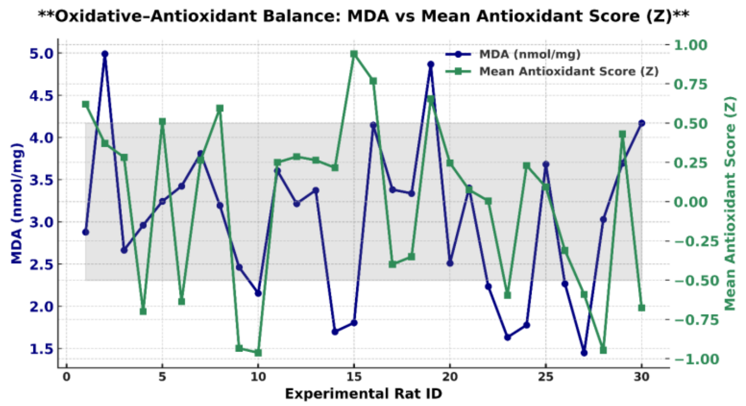

Figure 2 Oxidative-Antioxidant Balance: MDA vs Mean Antioxidant Score (Z).

Figure 2 represents the overall oxidative–antioxidant status of experimental rats, highlighting the dynamic relationship between lipid peroxidation and antioxidant defense. The navy line indicates renal malondialdehyde (MDA) concentration, an index of oxidative stress, while the green line represents the mean Z-score of major antioxidant enzymes (SOD, CAT, GPx, GSH). The grey-shaded region denotes the neutral oxidative–antioxidant balance zone (OABI =0 ± 0.5). Rats showing higher MDA values and lower antioxidant scores lie outside this balance zone, reflecting oxidative stress dominance and impaired antioxidant capacity. Conversely, animals within or near the neutral band maintain relative redox equilibrium. The figure visually demonstrates that oxidative stress and antioxidant activity are inversely related, supporting the protective influence of antioxidant mechanisms such as green-tea polyphenols against gentamicin-induced renal injury.

DISCUSSION

This study demonstrates that gentamicin induces significant oxidative stress in rat kidneys, as reflected by elevated malondialdehyde (MDA) levels and reduced antioxidant enzyme activities (SOD, CAT, GPx, GSH). Coadministration of green tea extract (GTE) mitigated these alterations, suggesting potent antioxidant and nephroprotective effects. These findings align with prior reports that oxidative stress is the principal mechanism of gentamicin-induced nephrotoxicity [17-19]. The observed rise in renal MDA and decline in antioxidant enzymes in the gentamicin-only group support earlier studies showing that gentamicin promotes lipid peroxidation while suppressing antioxidant defenses [20-22]. A study reported similar inverse correlations between MDA and renal antioxidants, confirming the oxidative nature of gentamicin injury [19]. Our results (r = –0.65 to –0.76) parallel these findings, reinforcing that excessive ROS generation overwhelms the enzymatic antioxidant system. In the present work, GTE administration reversed these biochemical changes. This agrees with Khan et al. who showed that green tea polyphenols restored SOD and CAT activity and reduced renal MDA in gentamicin-treated rats. Likewise, Abed et al. reported that GTE reduced MDA and enhanced SOD and GPx activities while improving renal histology [23,24]. The protective effects of green tea are attributed mainly to epigallocatechin-3-gallate (EGCG), which scavenges free radicals and activates Nrf2 signaling to upregulate endogenous antioxidants [25]. The histopathological findings in our gentamicin group, tubular degeneration, interstitial congestion, and hyaline casts, are consistent with those described by Bencheikh et al. and Aurori et al. who observed tubular necrosis and glomerular shrinkage accompanying elevated lipid peroxidation [2,26]. Remarkably, the GTE-treated group in our study exhibited restoration of standard tubular architecture, consistent with t2he renoprotective pattern described in other antioxidant interventions such as chrysin, formononetin, and biochanin A [27,29]. These parallels confirm that attenuation of oxidative stress correlates with structural renal recovery. Several studies corroborate our biochemical trends. Previous studies have demonstrated that flavonoids prevent gentamicin nephrotoxicity by activating the Nrf2/HO-1 pathway and enhancing SOD, CAT, and GSH levels [27,28]. Similarly, curcumin alleviated gentamicin-induced oxidative stress and apoptosis, while gallic acid reduced renal MDA and nitric oxide levels [30,31]. Oxymatrine and vitamin D have shown parallel antioxidant benefits, highlighting those multiple compounds converge on the exact protective mechanism, ROS suppression and antioxidant enzyme upregulation [32,33]. Although our findings generally agree with the literature, differences in the magnitude of antioxidant restoration were observed. For instance, some studies reported complete normalization of antioxidant markers with flavonoids such as chrysin [27]. In contrast, our GTE group showed partial recovery, possibly due to differences in dosage, bioavailability, or treatment duration. Another minor variation concerns superoxide dismutase activity: Medić-Brkić et al. observed reduced SOD despite lower MDA following chloroquine therapy, possibly due to altered redox signaling, whereas GTE in our study enhanced both SOD and CAT [34]. These variations underscore that antioxidant may differ in their mechanisms; some directly scavenge radicals; others induce endogenous enzymes. Clinically, these findings have important implications. Gentamicin remains a vital antibiotic, but nephrotoxicity limits its use. The demonstrated renoprotective effect of GTE suggests that antioxidant co-therapy may safely enhance gentamicin's therapeutic index. Green tea extract is inexpensive, well-tolerated, and widely available, making it an appealing adjunct in patients requiring aminoglycosides. Supporting this translational potential, Aksoz et al. showed that vitamin D supplementation protected against gentamicin nephrotoxicity via similar antioxidant and anti-inflammatory mechanisms [33].

LIMITATIONS

This study was limited by its small sample size and use of an animal model, which may restrict direct applicability to humans. Only biochemical and histopathological parameters were assessed, without exploring molecular mechanisms or signaling pathways. Additionally, a single dose and duration of green tea extract were used, which prevented the evaluation of dose-dependent effects.

CONCLUSION

In conclusion, this study demonstrates that gentamicin induces significant oxidative stress and renal damage in rats, characterized by elevated MDA levels and suppressed antioxidant enzyme activities. Administration of green tea extract (200 mg/kg/day) effectively mitigated these effects by reducing lipid peroxidation and restoring antioxidant balance, leading to notable histopathological improvement. These findings suggest that the antioxidant properties of green tea polyphenols, particularly EGCG, play a crucial protective role against gentamicin-induced nephrotoxicity. Green tea extract, therefore, holds promise as a safe and accessible adjunctive therapy to minimize oxidative kidney injury associated with aminoglycoside use.

RECOMMENDATIONS

Based on the study findings, it is recommended that future research explore different doses and treatment durations of green tea extract to determine optimal protective levels against gentamicin-induced nephrotoxicity. Molecular analyses should be included to elucidate the underlying antioxidant and signaling pathways, such as Nrf2 and NF-κB. Larger animal studies and clinical trials in humans are also warranted to confirm the translational potential of green tea extract as an adjunct therapy. Additionally, the combination of GTE with other natural or pharmacological antioxidants could be investigated to enhance renal protection and improve therapeutic outcomes.

FUNDING

No funding sources

CONFLICT OF INTEREST

None declared

ETHICAL APPROVAL

The study was approved by the Institutional Ethics Committee.

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