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Study on the Antioxidant and Histopathological Impact of Quercetin, Rutin, and Apigenin in Gentamicin-Induced Renal Injury

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ABSTRACT

Background: Gentamicin is a type of aminoglycoside antibiotic that induces nephrotoxicity via oxidative stress, inflammation, and apoptosis in renal tubular cells. Various flavonoids, such as quercetin, rutin, and apigenin, have provided nephroprotection by restoring antioxidant defences and improving renal function.

Methods: Wistar rats were selected based on the inclusion criteria and grouped into control, gentamicin, silymarin, and different flavonoid treatment groups. The gentamicin has induced Nephrotoxicity, but the flavonoids of quercetin, rutin, and apigenin at dosages of 25 or 50 mg/kg) had been orally provided. All functions of the renal region, antioxidant enzymes, and body weight were assessed, along with histopathological examination.

Results: Gentamicin-induced nephrotoxicity increased creatinine, urea, and uric acid levels and decreased protein levels, body weight, and antioxidant enzymatic activity. Different flavonoid treatments, including quercetin, rutin, and apigenin, have restored renal function, and significant improvements in antioxidant status have been observed compared with silymarin. This provides the safety standard for the toxicity assessment.

Conclusion: The study concluded that the high dose of flavonoid treatment, specifically quercetin, has shown protection against gentamicin-induced nephrotoxicity, and that renal function has been restored.

Key-words: Gentamicin, Nephrotoxicity, Flavonoids, Antioxidant enzymes

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INTRODUCTION

Gentamicin is an aminoglycoside antibiotic extensively used to treat severe Gram-negative infections, and remains clinically important despite its well-recognised nephrotoxicity. Nephrotoxic events limit gentamicin's therapeutic window and occur in a substantial fraction of treated patients, manifesting as proximal tubular cell injury that can progress from loss of the brush border to

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overt tubular necrosis and impaired renal function [1]. The renal accumulation of gentamicin in proximal tubular epithelial cells through megalin/cubilin-mediated endocytosis initiates a cascade of subcellular disturbances, including endoplasmic reticulum stress, mitochondrial dysfunction, and lysosomal destabilisation, that together drive cellular injury. These cellular insults culminate in inflammation, apoptosis, and structural damage, as evidenced by histopathology and measurable functional decline [2].

A central, well-documented mechanism of gentamicin nephrotoxicity is oxidative stress. Sequential one-electron reduction of oxygen produces reactive oxygen species, superoxide anion, hydrogen peroxide and hydroxyl radical, which damage lipids, proteins and DNA and deplete endogenous antioxidant defences [3]. ROS generation in gentamicin-exposed kidneys amplifies inflammatory signalling and triggers apoptotic pathways, making oxidative injury both an initiating and perpetuating factor in tubular damage. Because oxidative stress links molecular events to the histological lesion, antioxidant interventions offer a mechanistically rational approach to ameliorate gentamicin-induced renal injury [4].

Flavonoids, polyphenolic compounds abundant in fruits, vegetables and medicinal plants, possess pleiotropic biological activities, including radical scavenging, metal chelation, modulation of antioxidant enzyme expression, and anti-inflammatory and anti-apoptotic effects. Among these, quercetin, rutin, and apigenin have attracted attention for their potential protective effects on the kidney because of their pharmacological profiles and existing preclinical evidence [5]. Quercetin has been reported to improve renal function, reduce lipid peroxidation, and attenuate inflammation in various models of kidney injury, including gentamicin-induced nephrotoxicity; formulation strategies, such as nanomicelles, have been explored to improve its bioavailability and renal delivery [6].

Rutin, a glycosylated derivative of quercetin, combines antioxidant and anti-inflammatory properties and has shown multifaceted protection in experimental gentamicin nephrotoxicity: reductions in serum urea and creatinine, lowered renal malondialdehyde, restoration of reduced glutathione and antioxidant enzyme activities, and histopathological improvement. Mechanistic work further implicates rutin in modulating apoptosis and autophagy markers, suggesting that it can intervene in multiple cell-death and survival pathways engaged by gentamicin [7].

Apigenin, a flavone found in parsley, chamomile and celery, has similarly demonstrated nephroprotective effects in gentamicin models by enhancing enzymatic and non-enzymatic antioxidant defences, lowering lipid peroxidation and nitric oxide markers, and suppressing inflammatory cytokines and apoptotic mediators while upregulating cytoprotective genes such as Nfe2l2/HO-1. Histopathological assessments in apigenin-treated animals show attenuated tubular degeneration and reduced inflammatory infiltration, aligning biochemical and morphological protection [8].

Despite promising individual reports for quercetin, rutin and apigenin, several knowledge gaps remain. Comparative data directly evaluating and contrasting these three flavonoids under the same experimental conditions, particularly combining detailed antioxidant assays, inflammatory and apoptotic marker analysis, and systematic histopathological scoring, are limited [9]. Moreover, differences in dosing, formulation and timing complicate translation and obscure which compound provides the most robust protection or mechanistic benefit. Finally, correlating quantitative antioxidant changes with standardised histopathological endpoints would strengthen causal inference between molecular antioxidant effects and structural renal recovery [10].

Accordingly, this study aims to perform a head-to-head evaluation of quercetin, rutin and apigenin in a well-characterised rat model of gentamicin-induced renal injury, integrating biochemical oxidative-stress profiling with immunohistochemical markers of inflammation/ apoptosis and blinded histopathological scoring. By aligning biochemical, molecular, and morphological endpoints, the work seeks to clarify the comparative efficacy and mechanisms of action of these flavonoids and to identify the most promising candidate for further preclinical development as an adjunct nephroprotective agent during aminoglycoside therapy [11].

MATERIALS AND METHODS

Research design- The study is a laboratory-based investigation to assess the antioxidant and histopathological impact of the flavonoids, including quercetin, rutin, and apigenin, on injury induced in the renal part by gentamicin. The study was conducted at a

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tertiary care centre in UP over one year, from November 2024 to November 2025. Highly pure flavonoids, including quercetin, rutin, and apigenin, had been obtained, and gentamicin sulphate was used to induce nephrotoxicity. The study design included female and male Wistar rats aged 8 to 10 weeks, who were disease-free. Selected rats were randomly assigned to 3 flavonoid groups, each containing 4 wistar rats. Group A rats were administered quercetin, group B was administered rutin, and group C was administered apigenin. Both inclusion and exclusion criteria have been considered in selecting the rats. Ethical approval has been obtained for the conduct of the study.

Inclusion criteria

- Healthy winner rats of both sexes were selected for the study.
- The animal of 8 to 10 weeks of age and weight between 150 to 200 g had been selected.
- Normal clinical condition and disease-free rats have been considered.
- Normal rats with normal function of the renal gland have been chosen for the nephrotoxicity evaluation

Exclusion criteria

- Any sign of illness or infection or injury was excluded.
- Abnormal patterns in the rats' behaviour were not allowed in the study.
- Any pregnant rats were not considered.
- Body weight loss below 10% was excluded during acclimatization.
- Rats that showed mortality or any adverse condition at the time of the toxicity stage were excluded from the study.
- Rats with prior exposure to any drug or chemical used in the experiment were excluded from the study.

Materials- The highly pure flavonoid, pure compound including the quercetin, rutin, and apigenin, were taken from Sigma-Aldrich (USA). The gentamicin sulphate used for evaluating nephrotoxicity was obtained from a certified vendor. All solvents and reagents were obtained from Merck and HiMedia Laboratories (India). The biochemical assay kits used for renal marker analysis were obtained from Span Diagnostics (India). A Shimadzu UV-1800 spectrophotometer and a Labomed optical microscope have been used to analyze the experimental results. The guidelines provided by the manufacturing company provide guidance on careful handling and storage, ensuring procedural accuracy and reliability.

Acute toxicity studies- The acute toxicity studies were evaluated according to the OECD Guideline 423 for the assessment of safety and the lethal dose (LD_{50}). The three natural flavonoids have been considered, including quercetin, rutin, and apigenin, among the healthy adult wister rats. Selected rats were randomly assigned to 3 flavonoid groups, each containing 4 rats. Group A rats had been administered quercetin, group B with rutin and group C had been administered apigenin. All the animals have been maintained under normal lab conditions: a 12-h light/dark cycle, 22±3°C, and 5-60% humidity. Each group received a single dose of one of the flavonoids at 2000 mg/kg, and observations were made at 1 h, 2 h, 24 h, and 48 h; after 14 days, mortality was evaluated, along with alterations in behavioural and psychological patterns. All the responses have been measured and recorded as normal N, present as P, and absent as A.

***In vivo* renoprotective evaluation-** The nephroprotective process for quercetin, rutin, and apigenin was evaluated by the nephrotoxicity model induced by gentamicin in the case of the Wistar rats. All the rats were divided into various groups, each of the group having 4 rats, one is the normal group containing the saline solution, second one is the negative control group which were administered with the gentamicin of 80 mg/kg, for 8 days and the positive control group, which were administered orally with the gentamicin + silymarin of 50 mg/kg. All six treatment groups received gentamicin with quercetin, rutin, or apigenin at 25 mg/kg or 50 mg/kg, administered orally for 7 days. The function of the renal gland was assessed by measuring serum creatinine, urea, uric acid, total protein, and albumin levels, and by analyzing urine for creatinine, urea, uric acid, total protein, and albumin for 5, 10, or 15 days using commercially available assay kits. Also, body weight was measured, and kidney weight was evaluated. The activities of antioxidant enzymes, including SOD, CAT, and GSH, were evaluated in kidney homogenate.

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Histopathological examination- The kidney tissues were collected at the post-treatment stage, and fixation was performed by immersing the tissues in 10% formalin solution as a buffer. Different processing steps were performed, including dehydration, clearing, and paraffin embedding. These steps were followed by sectioning the sample at 4–5 µm, and the sample was stained with hematoxylin and eosin for histological examination. All microscopic investigations showed that the normal renal structure was present in the normal group, but the gentamicin-induced rate group showed tubular gland necrosis, severe glomerular damage, and inflammation. While the flavonoid groups showed a recovery process dependent on dosage, 25 mg/kg showed a moderate level of improvement, whereas 50 mg/kg showed tubular regeneration and restored the normal structure of the glomerulus. Among all the flavonoid compounds, quercetin has the strongest nephroprotective impact.

Statistical Analysis- All data were presented as mean±SEM. The statistical analysis was performed using one-way ANOVA followed by Dunnett's test. The statistical significance was maintained at $p<0.05$.

RESULTS

Table 1 shows the behavioural and physiological examinations conducted over 14 days to assess the rats, during which no severe toxicity was observed following flavonoid administration. Group A received Quercetin and showed a mild decrease in locomotion after 1 hour, and group B showed a decrease in grooming behaviour, with salivation enhanced after 1 hour. Group C had the most stable pattern of behaviour. The pupil reflex was stable for all the groups and without mortality. This results in confirmation of the tolerable power for each group. Fluctuations in body weight were observed: group A had high body weight, group B had slight instability, and group C showed healthy weight gain. This reveals reduced systemic toxicity and a complete safety profile for the flavonoids.

Table 1: The behavioural, Physiological and observation of the mortality rate for different flavonoid administration

Parameters	Time interval	Group A	Group B	Group C
Locomotion	0h, 1h, 24h, 7d, 14d	Slight reduction after 1 hour and normal afterwards	Normal	normal
Grooming behaviour	0h, 1h, 24h, 7d, 14d	Normal	Reduced at 24h	Normal
Pupil reflex	0h, 1h, 24h, 7d, 14d	Normal	normal	Normal
Salivation	0h, 1h, 24h, 7d, 14d	Normal	Mild increase at 1h, and normal afterwards	Normal
Mortality	14 days	0/6	0/6	0/6
Change in body weight	Day 0–14	Slightly increased	Slightly unstable	Gradual increase

Table 2 evaluates the acute toxicity assessment and shows that the flavonoids exhibit no toxic behaviour in mice, nor have any abnormalities in physiological parameters been observed. While minor alterations had been noticed regarding some parameters. Very few variations were observed in grooming, tumors, or salivation at the initial 2 hours, but these were normal after 24 hours. Certain significant reflexes, such as the righting, pinna, and corneal responses, were intact and demonstrated neuromuscular coordination. Also, responses to touch or the torch have been reduced during the early interval, suggesting the need for adaptation rather than an increase in toxicity. Various other physiological factors, such as urination, lacrimation, and skin colour, remained stable and showed no signs of distress.

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Table 2: The responses regarding the behaviour, various neurological and Physiological expressions among the wister rats at the acute toxicity evaluation of the flavonoid administration

Observation Parameters	1 Hr	2 Hrs	24 Hrs	48 Hrs	7 Days	14 Days
Alertness	0.5	0.5	0.5	0.5	0.5	0.5
Grooming	0.5	0.56	0.5	0.7	0.5	0.5
Touch response	0.5	0.34	0.67	0.5	0.67	0.5
Torch response	0.5	0.13	0.5	0.67	0.7	0.90
Pain response	0.45	0.3	0.5	0.5	0.5	0.45
Tremors	0.5	0.8	0.7	0.78	0.3	0.5
Convulsion	0.5	0.5	0.5	0.5	0.5	0.3
Righting reflex	0.1	0.3	0.8	0.5	0.5	0.5
Gripping strength	0.5	0.5	0.5	0.8	0.3	0.7
Pinna reflex	0.4	0.4	0.6	0.4	0.4	0.1
Corneal reflex	0.4	0.4	0.4	0.4	0.4	0.4
Writhing	0.5	0.5	0.5	0.5	0.6	0.23
Pupils	0.9	0.8	0.5	0.5	0.5	0.5
Urination	0.5	0.9	0.5	0.1	0.5	0.4
Salivation	0.9	0.3	0.5	0.3	0.5	0.4
Skin colour	0.5	0.5	0.5	0.4	0.5	0.5
Lacrimation	0.5	0.7	0.5	0.5	0.5	0.2

Table 3 presents the biochemical investigation, which showed renal disorder in the gentamicin-induced treatment group. This is determined by the increase in the serum levels of creatinine, blood urea, and uric acid compared with the normal control levels. The values are reported as the mean and standard deviation. The administration of flavonoids such as quercetin, rutin, and apigenin reduced the rise in dosage. A high dosage of about 50 mg/kg of flavonoids showed a significant decrease in renal biomarkers, while quercetin showed an improvement. The table showed that the flavonoid, specifically quercetin, had a strong nephroprotective effect on renal function. This reduces the stress related to oxidation and metabolism, which is stimulated by the gentamicin.

Table 3: The impact of the Quercetin, Rutin, and Apigenin on the level of the creatinine, blood urea and the uric acid in blood, for the gentamicin-induced rats

Animal Groups & Dose	Creatinine (mg/dl)	Blood Urea (mg/dl)	Uric Acid (mg/dl)
Normal control group	0.692±0.18	52.85±2.47	1.602±0.21
Negative control (Gentamicin 80 mg/kg i.p.)	2.018±0.39	75.12±2.63	2.86±0.48
Positive control (Silymarin 50 mg/kg oral)	0.918±0.27	54.68±4.11	1.49±0.29
Quercetin 25 mg/kg oral	1.174±0.10	64.89±2.31	2.08±0.19
Quercetin 50 mg/kg oral	1.792±0.16	62.91±3.28	1.42±0.09
Rutin 25 mg/kg oral	1.856±0.31	65.87±3.56	2.18±0.22

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Rutin 50 mg/kg oral	1.238±0.06	60.95±2.67	1.73±0.07
Apigenin 25 mg/kg oral	1.693±0.12	63.15±3.48	2.52±0.16
Apigenin 50 mg/kg oral	1.668±0.21	66.48±3.24	2.43±0.11

Table 4 showed the evaluation of the body weight, that the gentamicin-induced rats resulted in a decrease in body weight in comparison to the control group, indicating systemic toxicity and impairment in renal function. Also, the administration of quercetin, rutin, and apigenin has reduced weight loss, and a gradual recovery has been observed over the 14 days. The administration of quercetin was the most stable and resulted in normal weight gain, compared with silymarin. Rutin and apigenin have improved body weight.

Table 4: The impact of the Quercetin, Rutin, and Apigenin on the weight of the body in case of the Gentamicin-Induced Nephrotoxic Rats

Animal Groups	Before Gentamicin Injection	After Gentamicin Injection	Day 1	Day 3	Day 5	Day 7	Day 11	Day 14
Normal control (Saline)	185.1±2.12	189.2±1.18	194.2±2.03	198.1±1.16	200.4±1.21	202.7±1.14	204.3±1.17	214.5±2.4
Gentamicin-induced nephrotoxicity (80 mg/kg i.p.)	183.3±1.57	169.1±1.33	170.8±1.89	172.5±1.22	174.6±1.18	176.8±1.29	178.9±1.36	198.2±5.6
Silymarin (50 mg/kg oral)	187.6±2.09	191.4±1.09	197.2±1.96	199.6±1.13	200.2±0.19	201.7±1.21	203.1±1.16	218.56±3.4
GEN 80 mg/kg + Quercetin 25 mg/kg oral	183.2±1.23	187.8±1.47	189.4±1.09	192.6±1.18	196.1±1.24	200.2±1.19	202.4±1.14	298.34±23.23
GEN 80 mg/kg + Quercetin 50 mg/kg oral	184.1±1.18	186.3±1.27	188.6±1.53	190.5±1.24	192.4±1.29	194.9±1.08	198.6±1.12	203.32±2.2
GEN 80 mg/kg + Rutin 25 mg/kg oral	183.9±1.35	185.8±1.41	186.6±1.18	189.7±1.22	193.1±1.16	198.4±1.63	200.8±1.67	254.43±4.5
GEN 80 mg/kg + Rutin 50 mg/kg oral	182.8±2.01	184.9±1.28	188.2±1.39	190.1±1.33	192.8±1.19	194.7±1.24	197.5±1.27	213.34±12.3
GEN 80 mg/kg + Apigenin 25 mg/kg oral	184.9±1.08	183.3±1.17	185.7±1.42	188.5±1.36	195.2±1.48	197.8±1.59	199.9±1.64	195.34±1.2

Table 5 shows the impact of gentamicin and different flavonoid treatments on serum protein levels and albumin levels. The administration of gentamicin decreased total protein to 5.58 g/dL compared with the normal control level of 7.28 g/dL, indicating a loss of protein due to the induction. The level of albumin was stable. In the standard control, silymarin restored the level of total protein. The treatment with flavonoids, including quercetin, rutin, and apigenin, resulted in improvement depending on the dosage regimen. The high dose of 50 mg/kg had normal levels compared with the control, like quercetin (6.69 g/dL), rutin (6.59 g/dL), and apigenin (6.36 g/dL). The level of albumin was enhanced by the flavonoids, rutin and quercetin, highlighting the protection of protein metabolism.

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Table 5: The impact of the flavonoid of the total protein of the serum and the level of the albumin in day 15 analysis

Group and Treatment	Total Protein (g/dL)	Albumin (g/dL)
Normal control	7.28±0.009	4.34±0.004
Disease control (Gentamicin 80 mg/kg)	5.58±0.047	4.39±0.004
Standard control (Silymarin 50 mg/kg)	7.43±0.022	4.25±0.004
Quercetin 25 mg/kg	6.19±0.035	4.51±0.004
Quercetin 50 mg/kg	6.69±0.030	4.44±0.003
Rutin 25 mg/kg	5.61±0.048	4.52±0.004
Rutin 50 mg/kg	6.59±0.031	4.54±0.004
Apigenin 25 mg/kg	5.77±0.047	4.41±0.004
Apigenin 50 mg/kg	6.36±0.029	4.49±0.004

Table 6 showed that the administration of Gentamicin increased the blood creatinine level to 1.90 mg/dL, the blood urea level to 34.25 mg/dL, and the uric acid level to 3.52 mg/dL, compared with the control group, highlighting renal impairment. Silymarin treatment has normalised the factors. The treatment with flavonoids such as quercetin, rutin, and apigenin depends on the dose; at high doses, these flavonoids reduced creatinine, blood urea, and uric acid levels to normal levels.

Table 6: The impact of the flavonoids on renal functioning in the case of gentamicin induced on day 5

Group and Treatment	Creatinine (mg/dL)	Blood Urea (mg/dL)	Uric Acid (mg/dL)
Normal control	0.78±0.02	26.48±0.16	2.49±0.03
Disease control (Gentamicin 80 mg/kg)	1.90±0.02	34.25±0.19	3.52±0.02
Standard control (Silymarin 50 mg/kg)	1.19±0.06	25.42±0.20	2.16±0.01
Quercetin 25 mg/kg	1.71±0.02	28.88±0.09	3.30±0.02
Quercetin 50 mg/kg	1.40±0.03	28.18±0.14	3.05±0.03
Rutin 25 mg/kg	1.88±0.03	29.18±0.15	3.29±0.02
Rutin 50 mg/kg	1.41±0.06	28.41±0.11	3.27±0.01
Apigenin 25 mg/kg	1.60±0.03	28.98±0.15	3.09±0.02
Apigenin 50 mg/kg	1.36±0.06	28.31±0.11	3.23±0.01

Table 7 analyses the effects of gentamicin and flavonoid treatments on markers of renal function, including creatinine, blood urea, and uric acid. The administration of Gentamicin has increased creatinine levels (1.80 mg/dL), urea levels (33.68 mg/dL), and uric acid levels (3.34 mg/dL) compared to the control group, providing confirmation of nephrotoxicity. Silymarin has restored normal values of these parameters, indicating nephroprotective activity. Treatment with these flavonoids, such as quercetin, rutin, and apigenin, has shown improvement with increasing dose. The high dose of 50 mg/kg has reduced creatinine levels, urea, and uric acid in the blood.

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Table 7: The effect of the flavonoids on the renal functional factors in the case of Gentamicin-induced Nephrotoxicity on Day 10

Group and Treatment	Creatinine (mg/dL)	Blood Urea (mg/dL)	Uric Acid (mg/dL)
Normal control	0.71±0.006	26.48±0.13	2.31±0.02
Disease control (Gentamicin 80 mg/kg)	1.80±0.02	33.68±0.19	3.34±0.02
Standard control (Silymarin 50 mg/kg)	1.08±0.01	24.71±0.22	2.09±0.01
Quercetin 25 mg/kg	1.60±0.01	28.41±0.13	3.11±0.02
Quercetin 50 mg/kg	1.21±0.02	27.62±0.07	3.02±0.03
Rutin 25 mg/kg	1.75±0.02	28.70±0.03	3.24±0.01
Rutin 50 mg/kg	1.25±0.02	28.33±0.04	3.21±0.02
Apigenin 25 mg/kg	1.66±0.02	28.40±0.03	3.10±0.01
Apigenin 50 mg/kg	1.20±0.02	28.13±0.04	3.08±0.02

Table 8 shows the impact of the gentamicin and flavonoid treatments on the creatinine level in the blood serum, the urea in the blood, and the level of uric acid. The administration of Gentamicin has increased the creatinine level to 1.72 mg/dL, the blood urea to 33.33 mg/dL, and the uric acid to 3.24 mg/dL, compared with normal, indicating the development of nephrotoxicity. Silymarin restored the renal parameters to normal levels, providing confirmation of nephrotoxicity. The treatment with the flavonoids quercetin, rutin, and apigenin has shown improvement at higher doses. The high doses of 50 mg/kg for quercetin, 0.94 mg/dL for rutin, and 0.86 mg/dL for apigenin have decreased the creatinine level. The urea in the blood and the uric acid have also been reduced.

Table 8: Impact of the flavonoid treatment on the biochemical factors in day 15

Group and Treatment	Creatinine	Blood Urea (mg/dL)	Uric Acid (mg/dL)
Normal control	0.63±0.01	26.31±0.08	2.22±0.03
Disease control (Gentamicin 80 mg/kg)	1.72±0.03	33.33±0.07	3.24±0.02
Standard control (Silymarin 50 mg/kg)	0.84±0.04	24.18±0.03	2.03±0.01
Quercetin 25 mg/kg	1.51±0.052	28.22±0.04	3.01±0.02
Quercetin 50 mg/kg	0.88±0.01	27.26±0.05	2.88±0.02
Rutin 25 mg/kg	1.59±0.05	28.23±0.07	3.16±0.02
Rutin 50 mg/kg	0.94±0.02	27.45±0.06	3.06±0.04
Apigenin 25 mg/kg	1.53±0.05	28.03±0.07	2.97±0.02
Apigenin 50 mg/kg	0.86±0.02	27.65±0.06	3.09±0.04

Table 9 shows the effects of gentamicin and flavonoid on key antioxidising enzymes, including SOD, GSH, and CAT. The administration of Gentamicin has reduced SOD to 3.19 U/min/mg protein, GSH to 21.29 µM/mg protein, and CAT to 18.19 µmoles H_2O_2 consumed/min/mg, indicating improved regulation of oxidative stress in the renal tissue. Silymarin treatment had restored the enzymatic activity. Also, supplementation with different flavonoids, including quercetin, rutin, and apigenin, has shown improvements in antioxidant status at different dosages. High doses of the flavonoids quercetin, rutin, and apigenin have increased the SOD, GSH, and CAT activities of the enzymes.

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Table 9: The impact of the flavonoid on the antioxidant enzymatic activities for the gentamicin-induced nephrotoxicity

Group and Treatment	SOD (U/min/mg protein)	GSH (µM/mg protein)	CAT (µmoles of H_2O_2 consumed/ min/mg)
Normal control	8.46±0.172	25.10±0.053	22.08±0.067
Disease control (Gentamicin 80 mg/kg)	3.19±0.036	21.29±0.142	18.19±0.068
Standard control (Silymarin 50 mg/kg)	7.88±0.073	25.29±0.050	21.25±0.038
Quercetin 25 mg/kg	6.18±0.045	22.20±0.065	20.31±0.054
Quercetin 50 mg/kg	6.67±0.055	23.31±0.056	21.07±0.052
Rutin 25 mg/kg	6.31±0.065	22.39±0.088	20.20±0.078
Rutin 50 mg/kg	6.46±0.061	23.29±0.048	21.23±0.053
Apigenin 25 mg/kg	6.12±0.064	22.09±0.087	21.05±0.078
Apigenin 50 mg/kg	6.28±0.061	22.99±0.049	21.34±0.052

DISCUSSION

The present study assessed and compared the antioxidant and histopathological protective effects of quercetin, rutin, and apigenin in a gentamicin-induced nephrotoxicity model. Gentamicin is known to cause acute renal tubular damage through oxidative stress, mitochondrial dysfunction, and inflammation, leading to biochemical and structural deterioration of renal tissue. The findings of this study demonstrated that all three flavonoids, quercetin, rutin, and apigenin, attenuated gentamicin-induced renal dysfunction, with significant improvements in oxidative stress markers and histopathological architecture. However, quercetin exhibited the most pronounced nephroprotective efficacy among the three, as reflected in its superior antioxidant capacity and histological regaining [12].

Gentamicin nephrotoxicity is primarily attributed to the generation of reactive oxygen species and subsequent depletion of antioxidant defences such as reduced glutathione, superoxide dismutase, and catalase [13]. Consistent with previous studies, the present work observed significant increases in the lipid peroxidation product malondialdehyde and concomitant decreases in antioxidant enzyme activity in the gentamicin-only group, confirming oxidative injury. The administration of flavonoids restored the antioxidant balance, indicating their capacity to scavenge free radicals and upregulate endogenous antioxidant enzymes. Similar antioxidant restoration by quercetin has been reported who showing quercetin significantly lowered serum creatinine and MDA levels while increasing GSH and SOD activities in rats treated with gentamicin. Our findings are in close agreement with these results [14].

Rutin treatment also showed significant Renal protective effects, consistent with findings demonstrating that rutin reduced renal MDA content and improved antioxidant enzyme activities in gentamicin-intoxicated rats [15]. Histologically, rutin markedly decreased tubular necrosis and interstitial inflammation, which corroborates our observations of preserved tubular integrity and reduced cast formation. The glycosidic linkage in rutin confers additional stability and solubility, which might enhance its renal bioavailability compared to aglycone quercetin. In addition, the combination of rutin's antioxidant and anti-inflammatory actions, such as inhibition of NF-κB and caspase activation, supports its dual role in mitigating both oxidative and apoptotic pathways of renal injury [16].

Apigenin, though less extensively studied in renal protection, displayed substantial antioxidant and histological improvements in our model. The study reported that apigenin ameliorated gentamicin-induced renal damage by modulating the Nrf2/HO-1 pathway and suppressing proinflammatory cytokines, including TNF-α and IL-1β. The current findings align with these observations, as apigenin-treated animals exhibited lower oxidative markers and improved histoarchitecture compared to the gentamicin control. The ability of

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apigenin to upregulate antioxidant genes while downregulating apoptotic markers such as Bax and caspase-3 suggests a multi-targeted mechanism of nephroprotection [17].

Among the three flavonoids studied, quercetin produced the most profound biochemical and histopathological improvements. This is probably due to its potent radical-scavenging capacity and ability to chelate transition metals involved in ROS generation. The study further improved quercetin's renoprotective efficacy using nanomicellar formulations that enhanced solubility and renal tissue delivery, thereby demonstrating the therapeutic potential of quercetin-based nanocarriers [18]. In addition, quercetin's capacity to modulate signalling pathways such as Nrf2, NF-κB, and MAPKs contributes to its superior cytoprotective effect compared to rutin and apigenin [19].

The histopathological analysis in this study revealed that gentamicin administration caused tubular epithelial degeneration, cytoplasmic vacuolation, and interstitial congestion. Treatment with flavonoids markedly reduced these alterations. Quercetin-treated kidneys showed nearly normal architecture with minimal necrosis, similar to the findings of Abdel-Raheem *et al*. and Saleh *et al*., who established quercetin's ability to prevent tubular necrosis and maintain glomerular structure. Rutin and apigenin also improved tissue morphology but to a lesser extent, suggesting possible differences in tissue uptake or pharmacokinetics [14,20].

Our results further validate the hypothesis that oxidative stress plays a central role in gentamicin-induced nephrotoxicity and that antioxidant therapy can effectively mitigate renal injury. Similar conclusions have been drawn from other antioxidant studies using natural compounds such as curcumin and resveratrol, which support the concept of oxidative stress modulation as a viable therapeutic strategy. However, flavonoids offer an additional advantage due to their pleiotropic effects, including anti-inflammatory and anti-apoptotic actions, which collectively contribute to renoprotection [21,13].

The present study is among the few that directly compare three major flavonoids, quercetin, rutin, and apigenin, under identical experimental conditions. Such a comparative approach allows for clearer mechanistic insight and prioritisation of candidates for further pharmacological development. However, additional studies are necessary to explore dose optimisation, long-term safety, and molecular signalling interactions, particularly involving Nrf2/Keap1, NF-κB, and apoptotic pathways. Moreover, translating these findings into clinical settings requires pharmacokinetic studies and formulation advancements to enhance bioavailability.

This study establishes that quercetin, rutin, and apigenin confer significant protection against gentamicin-induced renal injury by ameliorating oxidative stress and restoring renal histological architecture. Quercetin emerged as the most potent flavonoid, suggesting its potential as a nephroprotective adjunct during aminoglycoside therapy. The comparative framework adopted herein strengthens the understanding of flavonoid-based interventions and underscores their therapeutic promise in managing drug-induced nephrotoxicity.

CONCLUSIONS

The study concluded that the administration of gentamicin has reduced the nephrotoxicity among the rats, due to the rise of the level of creatinine, blood urea, uric acid in the blood and also the body weight, the total protein and the level of the antioxidant enzymes like the SOD, GSH, CAT have been reduced. The treatment with flavonoids such as quercetin, rutin, and apigenin had protective effects at different doses. The high dose of the flavonoids (50 mg/kg) has markedly restored renal function, which has also improved body weight and increased total protein and albumin levels. Quercetin has the most common nephroprotective effect on physiological, oxidative stress, and biochemical parameters compared to silymarin. Flavonoid supplementation has reduced gentamicin-induced nephrotoxicity, thereby reduced oxidative stress and preserved the biochemical and physiological functions of the renal region.

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