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Original Article

Acyclovir-induced Nephrotoxicity: Protective Potential of N-acetylcysteine

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Abstract

Background and objectives: Oxidative stress could be a key process in acyclovir (ACV)-induced nephrotoxicity. N-acetylcysteine (NAC) is a water-soluble antioxidant with anti-inflammatory activity. This study aimed to evaluate the protective effect of NAC on ACV-induced nephrotoxicity in adult Wistar rats.

Methods: Forty adult male Wistar rats (200–220 g) were used. The rats were randomly divided into eight groups (n = 5/group) and were treated intraperitoneally daily for seven days as follows**:** Group 1 (Control) was administered water (0.2mL), while groups 2–4 were administered NAC (25, 50, and 100 mg/kg). Group 5 was administered ACV (150 mg/kg), while groups 6–8 were supplemented with NAC (25, 50, and 100 mg/kg) prior to treatment with ACV (150 mg/kg). On day 8, the rats were weighed and euthanized, and blood samples were collected for the assessment of biochemical markers. The kidneys were weighed and subjected to oxidative stress markers and histological evaluations.

Results: ACV had no significant ($p > 0.05$) effects on the body and kidney weights of rats compared to the control. ACV produced significant ($p < 0.001$) elevations in kidney malondialdehyde, serum urea, creatinine, and uric acid levels in rats, which differed from the control. There were significant ($p < 0.001$) decreases in kidney glutathione, superoxide dismutase, peroxidase, and catalase, as well as serum chloride, potassium, bicarbonate, and sodium levels in ACV-treated rats compared to the control. ACV caused widening of Bowman's space and tubular necrosis in the kidneys of rats. Nonetheless, NAC supplementation abrogated ACV-induced nephrotoxicity in a dose-dependent manner. Kidney histology was restored by NAC supplementation.

Conclusions: NAC protected against ACV-induced nephrotoxicity. This finding shows that NAC may have therapeutic potential for nephrotoxicity caused by ACV.

Introduction

The kidney contains numerous cell types arranged within the nephron, which serves as the functional unit of the kidney.[1] It is responsible for eliminating various drugs, chemicals, endogenous metabolites, and toxins.[2] The high rate of drug and toxin delivery to the kidney, due to its high renal blood flow (accounting for about 25% of cardiac output), exposes the kidney to elevated concentrations of these substances, which can lead to nephrotoxicity.[3] Drug-induced nephrotoxicity accounts for 8–60% of hospital-acquired kidney injuries[4] and 66% of cases of renal failure among the elderly.[5] The manifestations of drug-associated nephrotoxicity can occur in different forms, such as acute tubular necrosis, acute interstitial nephritis, and crystal nephropathy.[6]

Acyclovir (ACV) is an antiviral acyclic nucleoside analogue with activity against the herpes group of DNA viruses. Its antiviral activity involves conversion to triphosphate, which selectively inhibits herpes virus DNA polymerase.[7] ACV is generally a well-tolerated drug with remarkable clinical utility, but it can cause nephrotoxicity. Nephrotoxicity caused by ACV is typically characterized by decreased renal function, which develops within 12–48 h of administration. It can lead to crystal formation in the collecting tubules, causing obstructive nephropathy.[8] ACV-associated nephrotoxicity may also be accompanied by abnormal structural changes in the kidney.[9] Its nephrotoxicity can be exacer-

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bated by the presence of risk factors such as intravascular volume depletion, obesity, hypertension, and underlying renal disease.[10] In addition to obstructive nephropathy, some studies suggested that oxidative stress could play a role in the nephrotoxicity associated with ACV.[11]

N-acetylcysteine (NAC) is a water-soluble antioxidant and anti-inflammatory agent with a sulfhydryl moiety.[12] It is a molecule that easily penetrates membranes and rapidly diffuses through intracellular spaces. NAC acts as an antioxidant by increasing intracellular glutathione levels and directly scavenging reactive oxygen species (ROS) such as hypochlorous acid, superoxide, hydrogen peroxide, and hydroxyl radicals.[13] It has been shown to protect biomolecules from the harmful effects of oxidative stress[14] and enhance cellular antioxidant defenses. NAC is also a precursor for glutathione synthesis, which is essential for antioxidant function in cells.[15] NAC is commonly used to treat hepatotoxicity caused by acetaminophen overdose.[16] In animal studies, it has demonstrated a renal protective effect against nephrotoxicity induced by ifosfamide,[17] vancomycin,[18] and cisplatin.[19] Given the nephrotoxic effects of ACV and the limited treatment options available, the aim of the current study was to evaluate whether NAC can protect against ACV-induced nephrotoxicity in rats.

Materials and methods

Animals and drugs

Forty adult male Wistar rats (200–220 g), sourced from the animal house of the Department of Pharmacology and Toxicology, Faculty of Pharmacy, Niger Delta University, Nigeria, were used in this study. The rats were housed in cages at a temperature of 23 ± 1°C and humidity of 75 ± 5%, with a 12-h light/dark cycle and free access to food and water. The rats were acclimatized for two weeks prior to the study. Ethical approval (NDU/PHARM/PCO/AEC/062) was granted by the Research Ethics Committee of the aforementioned institution. This study adhered to the guidelines for the care and use of laboratory animals, 8th edition. ACV (Cipla Ltd., India) and NAC (Health Biotech Pvt. Ltd.) were used. All chemicals were of analytical grade.

Treatment protocol

The adult male Wistar rats (n = 40) were assigned to eight groups (n = 5/group) and treated daily with intraperitoneal drug injections for seven days as follows: Group 1 (Control) was administered water (0.2 mL/day), while groups 2–4 were administered NAC at doses of 25, 50, and 100 mg/kg,[20] respectively. Group 5 received ACV (150 mg/kg),[21] while groups 6–8 were supplemented with NAC (25, 50, and 100 mg/kg) 30 minutes before ACV (150 mg/kg) was administered.

Animal sacrifice

On day 8, the rats' weights were recorded, and they were anesthetized with ketamine (30 mg/kg, i.p.). Blood samples (7 mL) were collected from the heart, centrifuged (1,200 g for 20 m), and the sera were separated for renal function biomarker assessments. The kidneys were excised, weighed, rinsed in cold saline, homogenized in buffered (pH 7.4) 0.1 M Tris-HCl, and centrifuged (2,000 g for 20 m). The supernatants were assayed for markers of oxidative stress.

Determination of serum kidney function biomarkers

Serum concentrations of urea, bicarbonate, uric acid, creatinine, albumin, sodium, total protein, potassium, and chloride were measured using an autoanalyzer (Hitachi Model 7170, Tokyo, Japan).

Determination of kidney oxidative stress markers

Superoxide dismutase (SOD) was assayed as described by Sun and Zigman.[22] Glutathione (GSH) was evaluated according to the method of Sedlak and Lindsay.[23] Catalase (CAT) activity was measured as explained by Aebi,[24] while glutathione peroxidase (GPx) activity was evaluated according to the procedure described by Rotruck *et al.*[25] Malondialdehyde (MDA) was assessed using the method reported by Buege and Aust.[26]

Histology of the kidney

Excised kidneys were fixed in a 10% neutral formalin solution for 24 h. The kidneys were dehydrated in ascending concentrations of alcohol, embedded in paraffin blocks, and sectioned (4–5 µm thick) using a microtome. The sections were stained with hematoxylin and eosin for light microscopy. Microscopic images were captured using a Nikon Eclipse E200-LED (Tokyo, Japan).

Statistical analysis

Data were analyzed using two-way analysis of variance followed by the Tukey test. GraphPad Prism (Version 5.0, GraphPad Software Inc., La Jolla, California, USA) was used for statistical analysis. Results are presented as mean ± standard error of the mean, with significance set at $p < 0.05$, $p < 0.01$, and $p < 0.001$.

Results

Protective effect of N-acetylcysteine on the body and kidney weights of rats administered with acyclovir

The body and kidney weights of NAC-administered rats did not differ ($p > 0.05$) from the control group. No significant differences ($p > 0.05$) were observed in the body and kidney weights of ACV-administered rats when compared to the control. Additionally, the body-to-kidney weight ratio of ACV-treated rats did not differ ($p > 0.05$) from the control (Table 1).

Protective effect of N-acetylcysteine on kidney function biomarkers of rats administered with acyclovir

The effects of NAC on serum creatinine, uric acid, urea, electrolytes, total protein, and albumin levels were not significant ($p > 0.05$) when compared to the control (Fig. 1–5 and Table 2). In contrast, ACV significantly increased serum creatinine, uric acid, and urea levels, while decreasing serum total protein, electrolytes, and albumin levels, with significant differences from the control at $p < 0.001$ (Fig. 1–5 and Table 2). However, NAC supplementation significantly restored the serum levels of the aforementioned biomarkers in a dose-dependent manner at 25 mg/kg ($p < 0.05$), 50 mg/kg ($p < 0.01$), and 100 mg/kg ($p < 0.001$) when compared to ACV (Fig. 1–5 and Table 2).

Protective effect of N-acetylcysteine on kidney oxidative stress markers of rats administered with acyclovir

Kidney antioxidants (GSH, SOD, GPx, and CAT) and MDA levels did not differ ($p > 0.05$) from the control in NAC-administered rats (Table 3). In contrast, ACV significantly decreased ($p < 0.001$) kidney antioxidants and significantly ($p < 0.001$) increased MDA levels compared to the control (Table 3). However, NAC supplementation significantly restored kidney antioxidant and MDA lev-

Table 1. Protective effects of N-acetylcysteine on body and kidney weights of rats administered with acyclovir

Dose Mg/kg	Final body weight (g)	Absolute kidney weight (g)	Relative kidney weight (%)
Control	230.8 ± 18.0	0.65 ± 0.01	0.28 ± 0.03
NAC 25	220.7 ± 16.9	0.60 ± 0.02	0.27 ± 0.01
NAC 50	227.1 ± 16.9	0.65 ± 0.06	0.31 ± 0.07
NAC 100	220.7 ± 16.9	0.59 ± 0.04	0.29 ± 0.01
ACV 150	240.3 ± 11.0	0.66 ± 0.06	0.28 ± 0.07
NAC 25 + ACV 150	235.4 ± 16.7	0.71 ± 0.03	0.30 ± 0.09
NAC 50 + ACV 150	220.7 ± 14.4	0.69 ± 0.07	0.31 ± 0.03
NAC 100+ ACV 150	235.5 ± 16.7	0.69 ± 0.06	0.29 ± 0.05

Data presented as mean ± SEM, n = 5. ACV, acyclovir; ANOVA, analysis of variance and Tukey test; NAC, N-acetylcysteine; SEM, standard error of mean.

els in a dose-dependent manner at 25 mg/kg ($p < 0.05$), 50 mg/kg ($p < 0.01$), and 100 mg/kg ($p < 0.001$) when compared to ACV (Table 3).

Protective effect of N-acetylcysteine on kidney histology of rats administered with acyclovir

Normal kidney glomeruli and tubules were observed in control rats (Fig. 6a), while tubular necrosis, widened Bowman's space, and mesangial proliferations were observed in ACV-administered rats (Fig. 6b, c). Tubular necrosis and widened Bowman's space were observed in rats supplemented with NAC (25 mg/kg) (Fig. 6d). Rats supplemented with NAC (50 mg/kg) (Fig. 6e) showed tubular necrosis, while NAC (100 mg/kg) (Fig. 6f) showed normal glomeruli and tubules.

Discussion

Kidneys play essential roles in maintaining the homeostasis of water and electrolytes, biotransformation, and the excretion of drugs and their metabolites. Drug biotransformation and excretion can adversely affect the kidneys, leading to nephrotoxicity.[27] ACV, an antiviral drug eliminated by the kidneys, has been linked to nephrotoxicity, including acute tubular necrosis, obstructive nephropathy, and acute interstitial nephritis.[28,29] NAC is an anti-

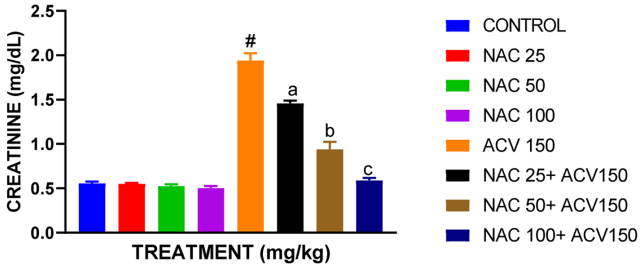

Fig. 1. Protective effect of N-acetylcysteine on serum creatinine of rats administered with acyclovir. Data presented as mean ± SEM, n = 5. $^{\#}p < 0.01$: Significantly different from the control. $^{a}p < 0.05$; $^{b}p < 0.01$, and $^{c}p < 0.001$: Significantly different from ACV. NAC, N-acetylcysteine; ACV, acyclovir; ANOVA, analysis of variance and Tukey test; SEM, standard error of mean.

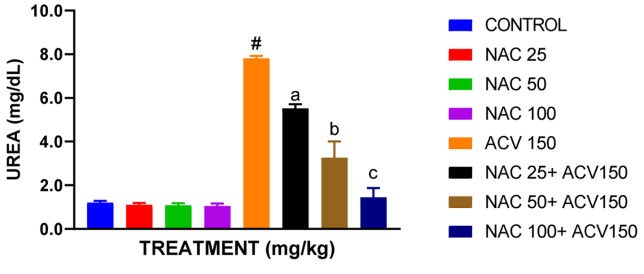

Fig. 2. Protective effect of N-acetylcysteine on serum urea of rats administered with acyclovir. Data presented as mean ± SEM, n = 5. $^{\#}p < 0.01$: Significantly different from the control. $^{a}p < 0.05$; $^{b}p < 0.01$, and $^{c}p < 0.001$: Significantly different from ACV. ACV, acyclovir; ANOVA, analysis of variance and Tukey test; NAC, N-acetylcysteine; SEM, standard error of mean.

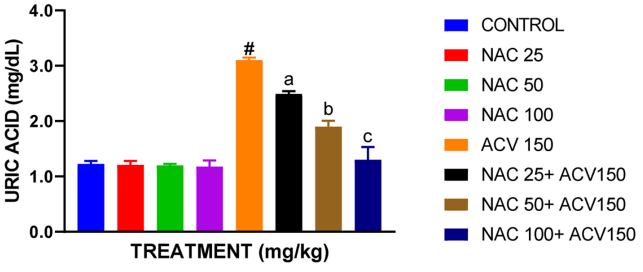

Fig. 3. Protective effect of N-acetylcysteine on serum uric acid of rats administered with acyclovir. Data presented as mean ± SEM, n = 5. $^{\#}p < 0.01$: Significantly different from the control. $^{a}p < 0.05$; $^{b}p < 0.01$, and $^{c}p < 0.001$: Significantly different from ACV. ACV, acyclovir; ANOVA, analysis of variance and Tukey test; NAC, N-acetylcysteine; SEM, standard error of mean.

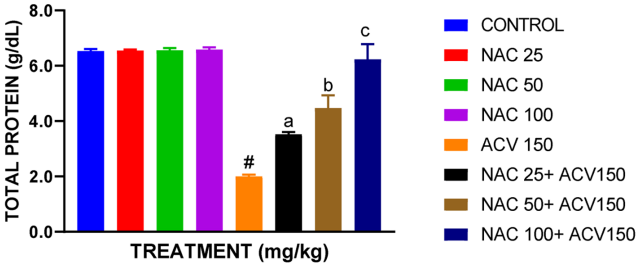

Fig. 4. Protective effect of N-acetylcysteine on serum total protein of rats administered with acyclovir. Data presented as mean ± SEM, n = 5. $^{\#}p < 0.01$: Significantly different from the control. $^{a}p < 0.05$; $^{b}p < 0.01$, and $^{c}p < 0.001$: Significantly different from ACV. ACV, acyclovir; ANOVA, analysis of variance and Tukey test; NAC, N-acetylcysteine; SEM, standard error of mean.

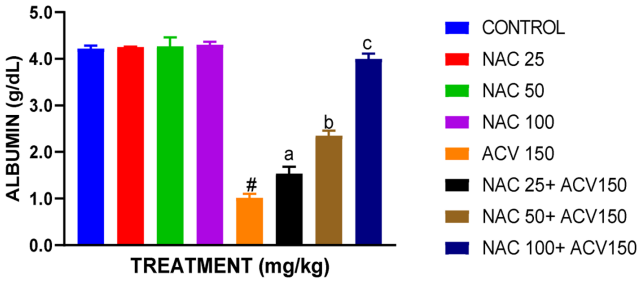

Fig. 5. Protective effect of N-acetylcysteine on serum albumin of rats administered with acyclovir. Data presented as mean ± SEM, n = 5. $^{\#}p < 0.01$: Significantly different from the control. $^{a}p < 0.05$; $^{b}p < 0.01$, and $^{c}p < 0.001$: Significantly different from ACV. ACV, acyclovir; ANOVA, analysis of variance and Tukey test; NAC, N-acetylcysteine; SEM, standard error of mean.

oxidant known for its renal protective effects in animal studies.[30] This study aimed to investigate whether NAC can prevent ACV-induced nephrotoxicity in rats. This study found no significant changes in the body or kidney weights of ACV-treated rats. This is consistent with the observations in rats treated with ACV (150 mg/kg/day) for 10 days.[12] However, it contradicts a study by Badawi, which reported decreased body and kidney weights in rats administered ACV (150 mg/kg) for 10 days.[31] It also differs from the findings in mice treated with ACV (150 and 600 mg/kg/day) as reported by Lu *et al.*[11] Additionally, the study found that ACV administration decreased serum total protein and albumin levels while increasing serum creatinine, uric acid, and urea. These observations suggest impaired renal function due to ACV exposure, similar to findings by Adikwu *et al.*[12] in rats treated with ACV (150 mg/kg/day) and by Xing *et al.*[32] in rats treated with ACV (100–600 mg/kg).

ACV is insoluble in urine and is filtered by the glomeruli and secreted by renal tubules. Studies have shown that decrease in urine flow rates, produces high ACV urine concentrations. Due to its insolubility, intratubular deposition of crystals occurs, obstructing the nephron, causing resistance to renal blood flow, and leading to the accumulation of creatinine, uric acid, and urea.[33] Urea crystal formation, attributed to aldehyde (an ACV metabolite), can directly damage renal tubules[34] and may have contributed to the altered serum kidney biomarkers observed in this study. However, NAC supplementation prevented ACV-induced alterations in albumin, creatinine, urea, total protein, and uric acid levels in a dose-dependent manner. These findings correlate with NAC's ability to restore serum levels of these renal markers in rats administered with ochratoxin A.[14] In this study, NAC restored serum creatinine, urea, and uric acid levels, probably by increasing urinary flow and promoting ACV excretion, thereby preventing ACV crystal deposition in the kidney tubules. Studies have shown that NAC can

Table 2. Protective effect of N-acetylcysteine on serum electrolytes of rats administered with acyclovir

Dose Mg/kg	Potassium (mmol/L)	Sodium (mmol/L)	Chloride (mmol/L)	Bicarbonate (mmol/L)
Control	5.37 ± 0.21	137.16 ± 12.6	112.33 ± 12.0	20.66 ± 2.53
NAC 25	5.34 ± 0.78	138.32 ± 10.2	114.21 ± 13.7	20.56 ± 2.09
NAC 50	5.31 ± 0.54	140.65 ± 11.9	116.82 ± 12.7	20.52 ± 1.76
NAC 100	5.30 ± 0.20	142.44 ± 10.7	119.84 ± 12.1	21.00 ± 1.76
ACV 150	2.01 ± 0.71$^{\#}$	51.01 ± 4.5$^{\#}$	35.9 ± 4.76$^{\#}$	12.5 ± 1.76$^{\#}$
NAC 25 + ACV 150	2.41 ± 0.34^{a}	70.12 ± 7.2^{a}	56.5 ± 6.21^{a}	17.8 ± 1.05^{a}
NAC 50+ ACV 150	3.67 ± 0.56^{b}	100.71 ± 10.7^{b}	70.02 ± 7.33^{b}	14.3 ± 1.70^{b}
NAC 100+ACV 150	5.00 ± 0.71^{c}	131.9 ± 12.1^{c}	101.61 ± 7.64^{c}	19.33 ± 3.64^{c}

Values presented as mean ± SEM, n = 5. $^{\#}p < 0.001$: Significantly different from the control. $^{a}p < 0.05$, $^{b}p < 0.01$, and $^{c}p < 0.001$: Significantly different from ACV. ACV, acyclovir; ANOVA, analysis of variance and Tukey test; NAC, N-acetylcysteine; SEM, standard error of mean.

Table 3. Protective effect of N-acetylcysteine on kidney oxidative stress markers of rats administered with acyclovir

Dose Mg/kg	MDA (nmole/mgprotein)	GSH (µmole/mgprotein)	CAT (U/mgprotein)	GPx (U/mgprotein)	SOD (U/mgprotein)
Control	0.25 ± 0.07	14.32 ± 1.98	29.92 ± 2.45	17.03 ± 1.32	29.87 ± 3.10
NAC 25	0.23 ± 0.01	14.34 ± 1.37	30.0 ± 2.54	17.12 ± 1.41	29.91 ± 2.16
NAC 50	0.22 ± 0.05	14.37 ± 1.00	30.12 ± 2.80	17.14 ± 0.77	30.10 ± 3.00
NAC 100	0.20 ± 0.03	14.40 ± 1.29	30.23 ± 2.34	17.27 ± 1.21	30.31 ± 2.34
ACV 150	1.46 ± 0.09$^{\pi}$	3.05 ± 0.16$^{\pi}$	11.42 ± 0.97$^{\pi}$	4.12 ± 0.81$^{\pi}$	10.40 ± 0.06 $^{\pi}$
NAC 25+ ACV 150	1.00 ± 0.05^{a}	5.67 ± 0.91^{a}	15.64 ± 1.46^{a}	7.25 ± 0.71^{a}	15.51 ± 0.28^{a}
NAC 50+ ACV 150	0.60 ± 0.05^{b}	9.33 ± 0.98^{b}	20.21 ± 1.76^{b}	11.32 ± 0.89^{b}	20.62 ± 2.55^{b}
NAC100+ACV 150	0.31 ± 0.02^{c}	13.21 ± 0.21^{c}	27.09 ± 2.19^{c}	15.54 ± 1.36^{c}	27.94 ± 3.62^{c}

Values presented as mean ± SEM, n = 5. $^{\pi}p < 0.001$: Significantly different from the control, $^{a}p < 0.05$, $^{b}p < 0.01$, and $^{c}p < 0.001$: Significantly different from ACV. ACV, acyclovir; ANOVA, analysis of variance and Tukey test; CAT, catalase; GPx, glutathione peroxidase; GSH, glutathione; MDA, malondialdehyde; NAC, N-acetylcysteine; SEM, standard error of mean; SOD, superoxide dismutase.

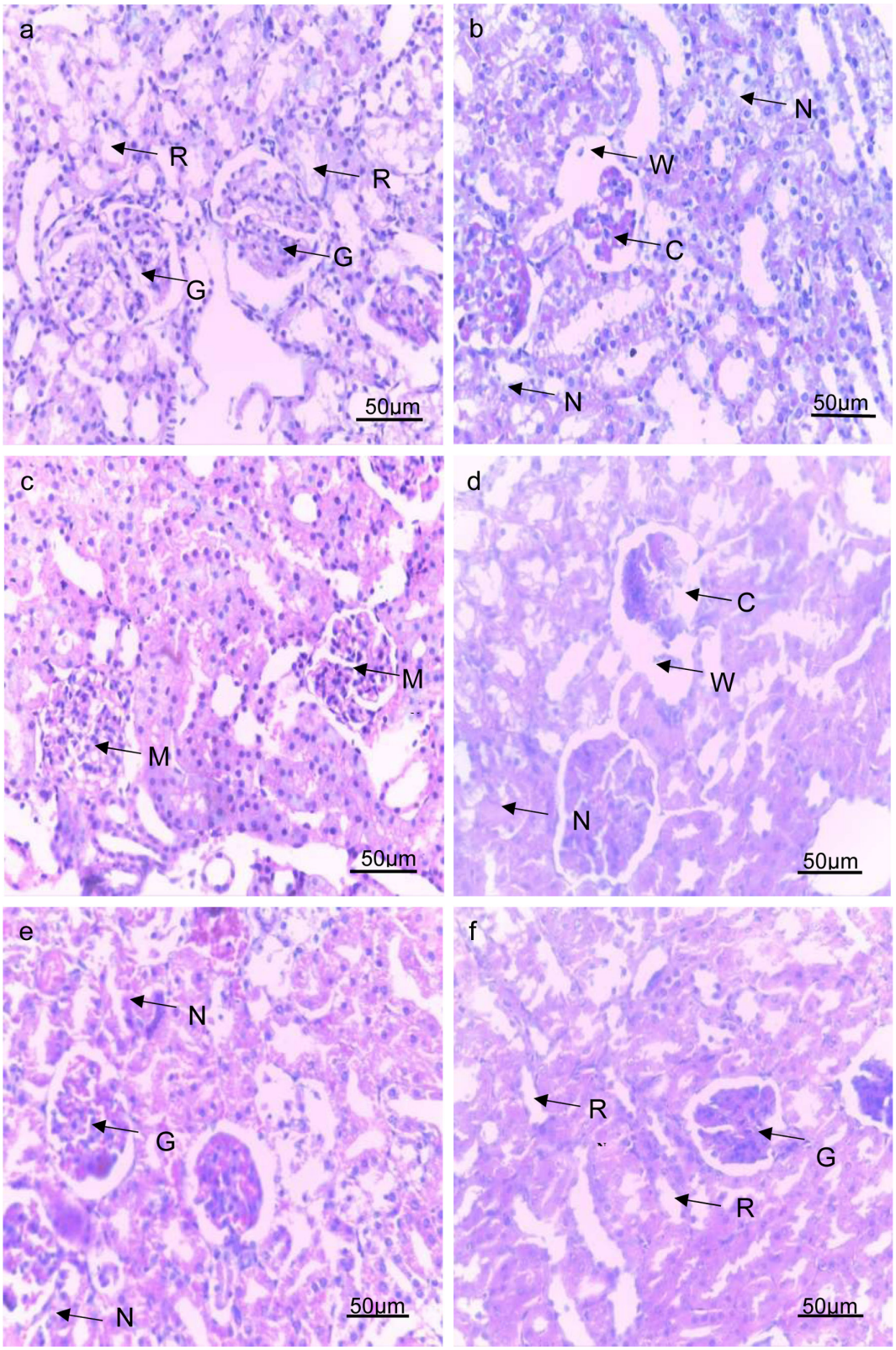

Fig. 6. Kidney micrographs. (a) Control; (b, c) Treatment with ACV (150 mg/kg); (d, e, f) Supplementation with NAC (25 mg/kg), NAC (50 mg/kg), and NAC (100 mg/kg), respectively. R, normal renal tubule; N, tubular necrosis; G, normal glomerulus; M, mesangial proliferation; C, collapsed glomerulus; W, widened Bowman's space. H and E × 400.

reduce renal vasoconstriction, improve renal flow, and reduce renal injury.[35,36] In this study, ACV altered serum electrolytes in rats, a finding similar to that reported in rats administered ACV (100 mg/kg/day).[21] ACV might have altered serum electrolytes by inhibiting the kidney's homeostatic function, leading to crystal deposition. However, NAC supplementation normalized serum electrolytes in a dose-dependent manner. This study also found that ACV decreased kidney antioxidants (SOD, GPx, CAT, and GSH) and increased MDA levels in rats, supporting similar findings in rats treated with ACV (150 mg/kg) for 10 days.[12] Badawi also reported decreased kidney antioxidants and increased MDA concentrations in rats treated with ACV (150 mg/kg) for 10 days.[31] These observations indicate that ACV induces oxidative stress.[12] Elevated MDA levels are indicative of ACV-induced kidney lipid peroxidation. Kidneys contain abundant long-chain polyunsaturated fatty acids, which are susceptible to ROS attack due to oxidative stress.[37] ACV may have caused oxidative stress in the kidneys by inducing excess ROS production, beyond the functional capacity of kidney antioxidants. This study demonstrated that NAC restored kidney antioxidant and MDA levels in a dose-dependent manner in rats administered with ACV. This is consistent with NAC's ability to stabilize kidney antioxidant and MDA levels in rats treated with vancomycin.[18] The restored kidney antioxidants in NAC-supplemented rats in this study can be attributed to NAC's ability to inhibit oxidative stress in the kidneys of ACV-treated rats. Furthermore, this study observed tubular necrosis, widened Bowman's space, and glomerular mesangial proliferation in ACV-administered rats, which supports previous observations by Yildiz *et al.* (2013)[38] and Badawi.[31] These findings may be attributed to damage to kidney biomolecules caused by ACV-induced oxidative stress. Oxidative stress can lead to cell necrosis and death due to its harmful impact on biomolecules (lipids, DNA, and proteins).[39] However, this study found that NAC supplementation restored kidney histology. This finding is consistent with previous studies which showed that NAC prevented kidney structural changes induced by cisplatin.[19] Studies have also shown that NAC protects renal tubules from damage, reduces renal cell death, and promotes cell healing through its antioxidant activity.[35,36] The renal protective effect of NAC against oxidative stress may involve several mechanisms, including its function as an ROS scavenger and a precursor for GSH synthesis, which enhances intracellular redox activity and increases the reductive status of protein thiols. Additionally, it can react with nitric oxide to form *S*-nitrosothiols with vasodilator properties.[40]

Future directions

There is a significant paucity of drugs to prevent ACV associated nephrotoxicity, but NAC showed a promising protective effect against ACV-induced nephrotoxicity in this study. However, this study has some limitations, which include the inability to evaluate some biochemical markers, including those that are related to inflammatory and signaling pathways, to buttress the findings of the current study from the molecular biology perspective. Also, quantitative histological study and the possible mechanism by which NAC protected against ACV- induced nephrotoxicity in Wistar rats were not evaluated in the current study. The aforementioned limitations warrant further studies. Additionally, clinical studies are suggested to validate these findings for possible clinical use.

Conclusions

This study demonstrated that NAC supplementation prevented ACV-induced nephrotoxicity in rats in a dose-dependent manner, indicating potential therapeutic value for ACV-associated nephrotoxicity.

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Conflict of interest

The authors have no competing interests.

Author contributions

Conceptualization (EA, BB, TBN, and KJ); experimental design (EA, BB, TBN, and KJ); acquisition of data (EA, BB, TBN, and KJ); data analysis (EA, BB, and KJ); writing – original draft (EA, BB, TBN, and KJ); critical revision of the manuscript (EA, BB, TBN, and KJ); funding of the research (EA, BB, TBN, and KJ); supervision (EA, BB, and KJ).

Ethical statement

Ethical approval (NDU/PHARM/PCO/AEC/062) was granted by the Research Ethics Committee of the aforementioned institution. This study adhered to the guidelines for the care and use of laboratory animals, 8th edition. ACV (Cipla Ltd., India) and NAC (Health Biotech Pvt. Ltd.) were used. All chemicals were of analytical grade. All animals received humane care to minimize suffering.

Data sharing statement

Data concerning this study can be obtained from the corresponding author as adikwuelias@gmail.com.

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