Original Article

Ameliorative Potential of Resveratrol on Kidney Toxicities Following Adjuvant Treatment with Antiretroviral Drugs in Male Wistar Rats

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ABSTRACT

Prolonged use of antiretroviral agents has been clearly associated with nephrotoxicity, suggesting deterioration of renal function in patients receiving Highly Active Antiretroviral Therapy (HAART). The present study was designed to investigate the therapeutic efficacy of resveratrol (RV) in the treatment toxins-induced renal impairment. Twenty-four adult male Wistar rats weighing 70–90 g were divided into four groups and subjected to the following treatments: Control A (distilled water), B (HAART), C (RV-2.5 mg/kg), D (RV- 2.5 mg/kg) + HAART. Assessment included renal histological examination; renal function indicators such as serum creatinine and blood urea nitrogen; serum electrolyte levels including sodium, chloride, potassium, bicarbonate; and oxidative stress biomarkers such as malondialdehyde, catalase and glutathione and superoxide dismutase. Adverse effects of HAART include adverse histological changes, such as tubular atrophy, vacuolization, tubular granular degeneration and glomerular capillaries abnormalities. Compared to the other treatment cohorts, serum creatinine, blood urea nitrogen (BUN), sodium, chloride and malondialdehyde (MDA) levels were significantly increased, while antioxidant enzyme activities such as catalase (CAT) and superoxide dismutase (SOD) and glutathione (GSH) levels were notably decreased. Renal structure remained largely unchanged after RV administration, with some recovery in histological abnormalities. Visible improvements, including reduced inflammation, reduced necrosis, reduced vacuolization and improved tubule and glomerular configuration, were also observed. In addition, RV notably increased antioxidant enzyme levels (SOD, CAT, and GSH) and decreased BUN, serum creatinine and MDA levels. RV helped mitigate HAART-induced structural abnormalities and renal dysfunction, while improving renal morphology. However, further investigation of these mechanisms is needed.

Keywords: HAART; Resveratrol; Nephrotoxicity; Antioxidant; Wistar Rats

1. Introduction

The use of Highly Active Antiretroviral Therapy (HAART) has significantly improved the quality of life of people living with HIV/AIDS, as evidenced by recent research findings (1, 2). Studies suggest that adherence to HAART and achieving of an undetectable viral load have mutually beneficial effects on quality of life, which encompasses multiple domains such as physical health, psychological well-being, social relationships, and environmental factors (3). In addition, robust immunosuppressive control and overall health-related quality of life can be supported by regular use of HAART (4). Overall, the development and implementation of highly active antiretroviral drugs has contributed significantly to improving both the quality of life and life expectancy of people living with HIV/AIDS (5).Antiretroviral medications have significantly reduced the incidence of kidney disease in people infected with the human immunodeficiency virus (HIV), offering a substantial reduction in HIV-related kidney complications by up to 90% (6). However, prolonged use of these medications increases the risk of kidney failure (7). HIV - associated Kidney diseases have gradually become a primary renal concern among HIV-positive individuals, largely due to drug-induced nephrotoxicity, particularly from HAART (8). Although HAART treatment is generally supportive of renal function, it can also lead to kidney failure through various mechanisms, including acute tubular necrosis, interstitial nephritis, and crystal nephropathy (9). Patients with HIV receiving HAART may experience a decline in renal function parameters including estimated Glomerular Filtration Rate (eGFR) and Creatinine Clearance (CrCl) (10). Antiretroviral therapy may induce or exacerbate kidney failure in the HIV-population, with common causes of acute kidney injury (AKI) including drug toxicity, volume depletion, sepsis, and liver-related conditions (11). Renal function at the initiation of antiretroviral therapy is a robust predictor of mortality, particularly in individuals with a history of AIDS (12). Research has demonstrated the effective anti-HIV properties of natural antioxidants, which are attributed to their regulation of the immune system, inhibition of key enzymes involved in HIV replication, and antioxidant properties (13). However, the limited bioavailability of antioxidants limits their clinical utility (14). Recent studies have focused on the use of natural remedies to alleviate the effects of antiretroviral therapy (ART) and HIV infection, including modulation of lipid metabolism and reduction of oxidative stress levels (15). Overall, resveratrol is a promising natural intervention for protecting cells from free radical-induced damages, with potential applications across a spectrum of health conditions. Resveratrol, a naturally occurring phytophenol found in many plants, is most abundant in grape-derived products such as red wine (16). Its properties include antioxidant capacity and the ability to neutralize free radicals, thereby mitigating oxidative stress (17). Extensively studied in clinical trials, resveratrol shows promise in improving the prognosis of several diseases, such as diabetes, obesity, cancer, Alzheimer's disease, stroke, and cardiovascular diseases (18). Resveratrol has demonstrated potential in mitigating renal toxicity, reducing resveratrol has been observed to reduce serum creatinine and BUN levels, alleviating oxidative stress, elevate antioxidant enzyme levels, increasing histopathological changes in animal models of kidney failure (19). It protects against renal failure and hypertension in an adenine-induced model of chronic kidney disease (CKD) (20). Similarly, resveratrol therapy has been shown to upregulate endogenous Klotho activity, which provides anti-apoptotic effects and protects against acute kidney injury induced by sepsis (21). Resveratrol supplementation improves endothelial function in patients with CKD, thereby benefiting cardiovascular health (22). In addition, resveratrol has been shown to positively influence renal function outcomes in animal models of acute kidney injury, particularly at low doses and short intervention periods (19). Furthermore, resveratrol has emerged as a potential anti-aging agent for the kidneys due to its ability to modulate various signaling pathways and delay the aging process (23). Therefore, we aimed to evaluate the therapeutic efficacy of resveratrol in the treatment of renal failure resulting from antiretroviral toxicity.

2. Materials and Methods

2.1. Animal Care

Twenty-four (24) male Wistar rats weighing 70–90 g were used in this study. The animals were housed in Animal House facilities at the University of Afe Babalola in Ado-Ekiti, Nigeria. Adherence to established protocols for the management and welfare of laboratory animals was strictly followed in all procedures involving animal handling (24). The research protocol was approved by the Animal Ethics Committee (protocol number: AB/EC/17/01/159). The rodents were subjected to a uniform schedule of food and water consumption, maintained on a 12-hour diurnal cycle, and acclimated for a period of two weeks for acclimatization.

2.2. Experimental design

2.2.1. Grouping of animals

Subjects were randomly assigned to four clusters (A-D), each containing six rats: Group A (control/placebo cluster) received distilled water. Group B received a combination of zidovudine, lamivudine, and nevirapine (HAART). Group C received a dosage of 2.5 mg/kg of

resveratrol (RV), while Group D received 2.5 mg/kg RV in addition to HAART.

2.2.2. Drug Preparation and Administration

The HAART medication Zidovex LN, consisting of zidovudine, lamivudine, and nevirapine (25), was obtained from the Federal Teaching Hospital in Ido-Ekiti, Nigeria. Calculation of appropriate doses for animals was based on the therapeutic dose equivalent for humans, as determined using a rat model (26). Resveratrol was purchased from Infinite Age Co. (Tacoma, USA). Zidovudine, lamivudine, and nevirapine at human therapeutic equivalent doses of 600, 300, and 400 mg/day, respectively, comprised the HAART cocktail. This mixture was diluted in 100 mL of distilled water and adjusted to animal doses of 1.33, 0.66, and 0.89 mg/kg body weight (27). All treatments were administered orally once daily for six weeks.

2.2.3. Determination of Body Weight

Rats were weighed before start of the intervention, weekly, ,and on the day of the experiment. Body mass was evaluated between 8:00 a.m. to 10:00 a.m. using an electronic scale (HX-302 T, HX-T electronic weighing balance, China).

2.2.4. Sample Collection

Cervical dislocation and euthanasia were performed on day 43 (27). Three milliliters (mL) of blood were collected from the cardiac region via cardiac puncture and allowed to coagulate for two hours in conventional tubes. After centrifugation at 1000 × g for 15 min, the resulting liquid layer (referred to as serum) was collected for biochemical analysis (26).

2.3. Organ Weight

The Kidney Weight (KW) was measured after removal of fat. A digital balance (HX-T electronic weighing balance, HX-302 T, China) was used for this purpose. Each kidney was assessed separately, and each measurement (KW) was recorded in grams (g). The mean value of each kidney was calculated (28).

2.4. Organ Index

The following calculations were used to determine the weight of each kidney:

Relative Kidney Weight = (Absolute kidney weight /Total body weight) × 100%

2.5. Histological examination

Kidney tissue samples were examined microscopically after fixation in 10% neutral buffered formalin. Thin slices of 5 µm thickness were cut on using a rotary microtome (Microm GmbH, serial no. 42861, CAT. no. 02100). Hematoxylin and eosin (H&E) staining is commonly used to assess tissue architecture (29). A histopathology specialist blinded to the study methodology reviewed the slides.

2.6. Renal function tests

2.6.1. Measurement of Serum Creatinine and Blood Urea Nitrogen

Serum Creatinine (Cr) and Blood urea nitrogen (BUN) levels were determined in serum samples. According to Ochei and Kolhatkar (30), blood urea nitrogen/serum urea and creatinine concentrations were analyzed by the diacetylmonoxime technique and Jaffe reaction, respectively.

2.6.2. Measurement of Serum Electrolytes

Bicarbonate (HCO3) was evaluated through titration, while the flame photometer technique was used to quantify potassium (K+) and sodium (Na+) levels in the serum (30). Chloride (Cl) concentration was assessed using a spectrophotometric approach (31).

2.7. Parameters of Oxidative Stress and Lipid Peroxidation

2.7.1. Determination of renal serum malondialdehyde (MDA) concentration

Quantification of serum malondialdehyde (MDA) levels was performed according to the procedure described by Albro and Corbett (32), using thiobarbituric acid (TBA) and a mixture of hydrochloric acid (HCl) and trichloroacetic acid (TCA) at fixed concentrations (0.37% TBA, 0.25N HCl, and 15% TCA). Specifically, one milliliter of serum was incubated, cooled, and centrifuged for 15 minutes. The absorbance of the resulting clear supernatant was measured at 535 nm in relation to a reference blank.

2.7.2. Determination of Renal Serum Reduced Glutathione (GSH) Concentration

The analysis was performed on blood samples according to the protocol described by Sedlak and Lindsay (33),with slight modifications. The method is based on protein precipitation in a sulfuric acid/tungstate solution and the subsequent formation of a yellow color due to interaction with 5, 5'-dith-iobis-2-nitrobenzoic acid (DTNB). Absorbance was recorded at 412 nm for 30–60 s and compared with the control. Glutathione concentrations (GSH) were calculated using a standard curve for GSH.

2.7.3. Measurement of Serum Superoxide Dismutase (SOD) Concentration in the Kidney

Superoxide dismutase (SOD) was measured according to the procedure outlined by (34). Briefly, 0.1 mL of serum (1:10) was diluted in 0.9 mL of distilled water to obtain a microsome dilution. An aliquot was prepared by combining the diluted microsome (2.5 milliliters) with 0.05 M carbonate buffer (0.2 mL). Adrenaline (0.3 mM adrenaline was then added to initiate the process. 0.05 M carbonate buffer in 2.5 mL mL , 0.3 mL adrenaline in 0.3 mM, and 0.2 mL distilled water were used as reference

solutions. Absorbance was measured between 30 and 150s at a wavelength of 480 nm.

2.7.4. Determination of serum catalase activity in the kidney

The determination of serum catalase (CAT) activity was performed according to the protocol described by Aebi (35). 2.80 mL mLof 50mM potassium phosphate buffer (pH 7.0) and 10µl of serum were added to the test tube. The reaction was initiated by the addition of 0.1 mL mLof freshly prepared 30 mM H2O2, and the rate of H2O2 decomposition was monitored using a spectrophotometer for five minutes at 240 nm.

2.8. Statistical Analysis

Morphometric data were examined using conventional parametric analyses on Graph Pad Prism version 5.00 for Windows. After conducting one-way analysis of variance (ANOVA) and Tukey's post hoc test, the results were presented as the mean ± standard error of the mean (GraphPad Software, San Diego, CA, USA), with a significance threshold set at $p < 0.05$.

3. Results

3.1. Organ Body Weight Changes

The final body weight of each experimental group showed a marginal increase, with Group B showing the highest increase and Group D showing the lowest one. Comparable kidney weights (KW) and relative kidney weights (KW/BW × 100) were observed in all groups, with no statistically significant differences between them ($P < 0.05$) (Table 1).

3.2. Histopathological examination of the kidney tissue

The kidney cross-sections of groups A and D showed minimal histological changes and well preserved cytoarchitecture. Absence of inflammation in the interstitium, typical morphology of proximal and distal convoluted tubules (PCT and DCT), intact glomeruli (G), glomerular mass, and membranes were observed. Conversely, HAART-treated group B rats showed obvious adverse histological changes, including tubular atrophy, vacuolization, interstitial inflammation, tubular granular degeneration, irregularities in glomerular capillaries, and increased glomerular space. In contrast, group D rats treated with HAART and RV, showed fewer inflammatory cells, less necrosis, less vacuolization, and improved tubular and glomerular structure (Figure 1).

3.3. Changes in Blood Urea Nitrogen (BUN) levels

In contrast to placebo group A, group B showed significantly elevated BUN levels ($p < 0.001$). Co administration of RV + HAART resulted in a significant decrease in BUN levels in group D ($p < 0.05$), in contrast to those observed in group B (Table 2).

3.4. Changes in Serum Creatinine (Cr) Levels

Group B showed significantly elevated creatinine levels ($p < 0.05$) compared to the control group, whereas Group D showed a significant decrease ($p < 0.05$) in this criterion after adjunctive HAART therapy with resveratrol (Table 2).

3.5. Changes in Serum Electrolytes Concentrations

Serum sodium and chloride levels were statistically significant ($p < 0.05$), with greater concentrations observed in group B compared to group A. In addition, the potassium levels were elevated in group B was elevated compared to control group A, although the difference was not remarkable ($p < 0.05$). Notably, the differences in serum bicarbonate concentrations between groups were not statistically significant ($p < 0.05$) (Table 3).

3.5.1. Malondialdehyde

The data presented in Figure 2A show a remarkable difference in the mean serum MDA concentration of HAARTgroup B (44.5 ± 2.43 $x10^2$µmol/L) compared to Control group A (25.6 ± 1.16 $x10^2$µmol/L) with statistical significance ($p<0.001$). In addition , MDA levels in group D showed a significant increase compared to the control group ($p<0.01$) and group C receiving resveratrol ($p<0.05$). RV groups C and D (RV + HAART) had mean serum MDA concentrations of (29.5 ± 2.63$x10^2$µmol/L) and (39.9 ± 2.42 $x10^2$µmol/L), respectively.

3.5.2. Superoxide dismutase

Figure 2B shows the average activity of the superoxide dismutase enzymes. The levels of SOD showed a significant decrease ($p<0.05$) after HAART treatment in group B (0.73 ± 0.03U/mL) in contrast to the control group A (1.50 ± 0.25U/mL). Conversely, group receiving RV treatment, showed a significant increase ($p<0.05$) with levels of 2.2 ± 0.18U/mL compared to group A. Furthermore, a significant increase ($p<0.05$) was observed in the RV + HAART concurrent treatment group D (1.40 ± 0.3U/mL) compared to group B receiving HAART alone.

3.5.3. Catalase

Figure 2C shows the mean serum catalase activity. The HAART administration in Group B (16.9 ± 1.28U/mL) resulted in a significant decrease ($p<0.01$) in CAT levels compared to the control group A (24.8 ± 0.98U/mL). Group C, treated with RV (33.8 ± 1.75 U/mL), showed significantly increased ($p<0.001$) in catalase activity compared to control group A. Similarly, the introduction of RV therapy in group D (24.6 ± 1.13 U/mL) resulted in a significant increase($p<0.01$) in CAT levels compared to HAART group B. Notably, group D, receiving RV + HAART adjuvant treatment, experienced a significant decrease ($p<0.001$) in CAT levels compared to the RV-treated group C.

3.5.4. Reduced Glutathione

Treatment with RV resulted in significant increase in GSH levels within group D (4.08 ± 0.27 mmol/mL) compared to the HAART treated group B (2.92 ± 0.33 mmol/mL) with statistical significance ($p < 0.05$). The mean glutathione levels for groups A and C were measured to be 3.93 ± 0.27 mmol/mL and 4.25 ± 0.21 mmol/mL, respectively, as shown in Figure 2D.

Table 1: Body weight, kidney weight, and relative kidney weight

Groups	Initial BW (g)	Final BW (g)	Weight diff (g)	Difference (%)	KW (g)	KW/BW x 100
A	152 ± 3.39	212 ± 4.55	60	39.5	1.32 ± 0.04	0.62
B	152 ± 3.76	219 ± 3.24	67	44.1	1.32 ± 0.04	0.60
C	154 ± 3.27	216 ± 3.42	62	40.3	1.24 ± 0.02	0.57
D	158 ± 2.87	209 ± 3.47	51	32.2	1.35 ± 0.04	0.65

Data are presented as mean ± SEM ($p<0.05$ was used to compare all results); A, B, C, and D represent the Control, HAART, RV, and RV+HAART groups, respectively. The comparison groups were B, C, D versus A; D versus B; and D versus C.

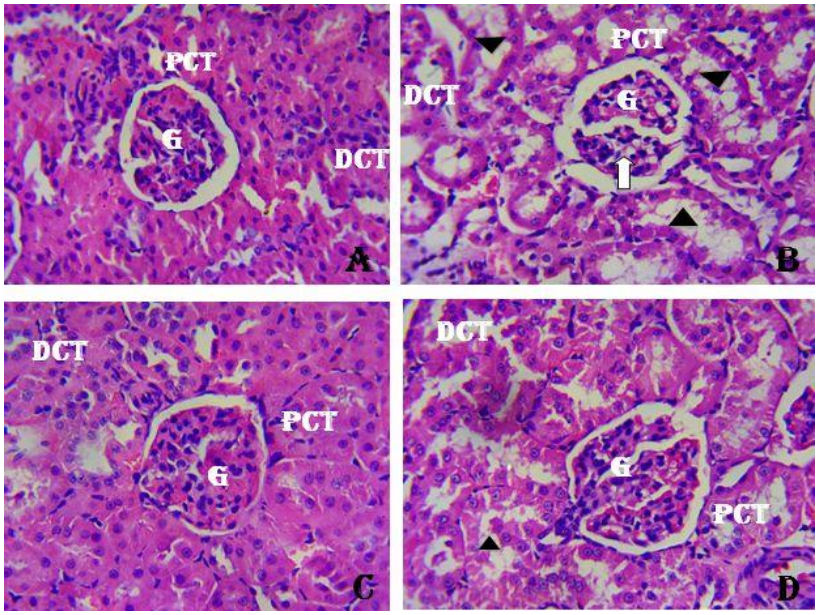

Figure 1: The histoarchitecture of kidney sections from groups A–D is depicted in a photomicrograph. The kidney sections of group A (control) demonstrated well-preserved glomerular and tubular architectures. Group B (HAART) exhibited significant glomerular irregularities, tubular atrophy, vacuolization, and cellular degeneration. In contrast, group C (RV) showed kidney histology that closely resembled that of the control group, characterized by minimal hypocellularity. Group D (HAART + RV) showed moderate atrophy of the glomerulus tuft, necrosis in certain renal tubules, and signs of regeneration in other renal tubules. The samples were stained with hematoxylin and eosin (Mg × 400). (G: Glomerulus; PCT: Proximal convoluted tubules; DCT: Distal convoluted tubules; white arrow, glomerular degeneration; black arrowhead, tubular degeneration).

Table 2: Blood urea nitrogen (BUN) and serum creatinine (Cr) levels

Groups	BUN(mg/dl)	Cr(mg/dl)
A	16.9 ± 0.62	3.1 ± 0.51
B	24.8 ± 2.02[a]	6.3 ± 0.67[c]
C	16.5 ± 0.46	3.3 ± 0.51
D	18.7 ± 0.63[b]	3.5 ± 0.77[d]

Data are presented as mean ± SEM ($p<0.05$ was used to compare all results); A, B, C, and D represent the Control, HAART, RV, and RV+HAART groups, respectively. The comparison groups were B, C, D versus A; D versus B; and D versus C. For BUN: [a]($p<0.001$)B vs A; [b]($p<0.001$)D vs B; For Cr: [c]($p<0.05$)B vs A; [d]($p<0.05$)D vs B

Table 3: Serum electrolytes concentration

Groups	Na^+(mmol/l)	K^+ (mmol/l)	HCO3 (mmol/l)	Cl (mmol/l)
A	70.0 ± 0.91	3.57 ± 0.93	156 ± 9.70	65.2 ± 4.02
B	84.8 ± 4.59[e]	5.62 ± 0.69	201 ± 14.90	91.9 ± 7.36[f]
C	69.5 ± 0.95	4.97 ± 0.80	177 ± 27.10	67.4 ± 6.62
D	73.7 ± 3.79	4.51 ± 0.43	208 ± 19.20	80.2 ± 5.62

Data are presented as mean ± SEM ($p<0.05$ was used to compare all results); A, B, C, and D represent the Control, HAART, RV, and RV+HAART groups, respectively. The comparison groups were B, C, D versus A; D versus B; and D versus C. For Na^+ : [e]($p<0.05$)B vs A ; For Cl : [f]($p<0.05$)B vs A

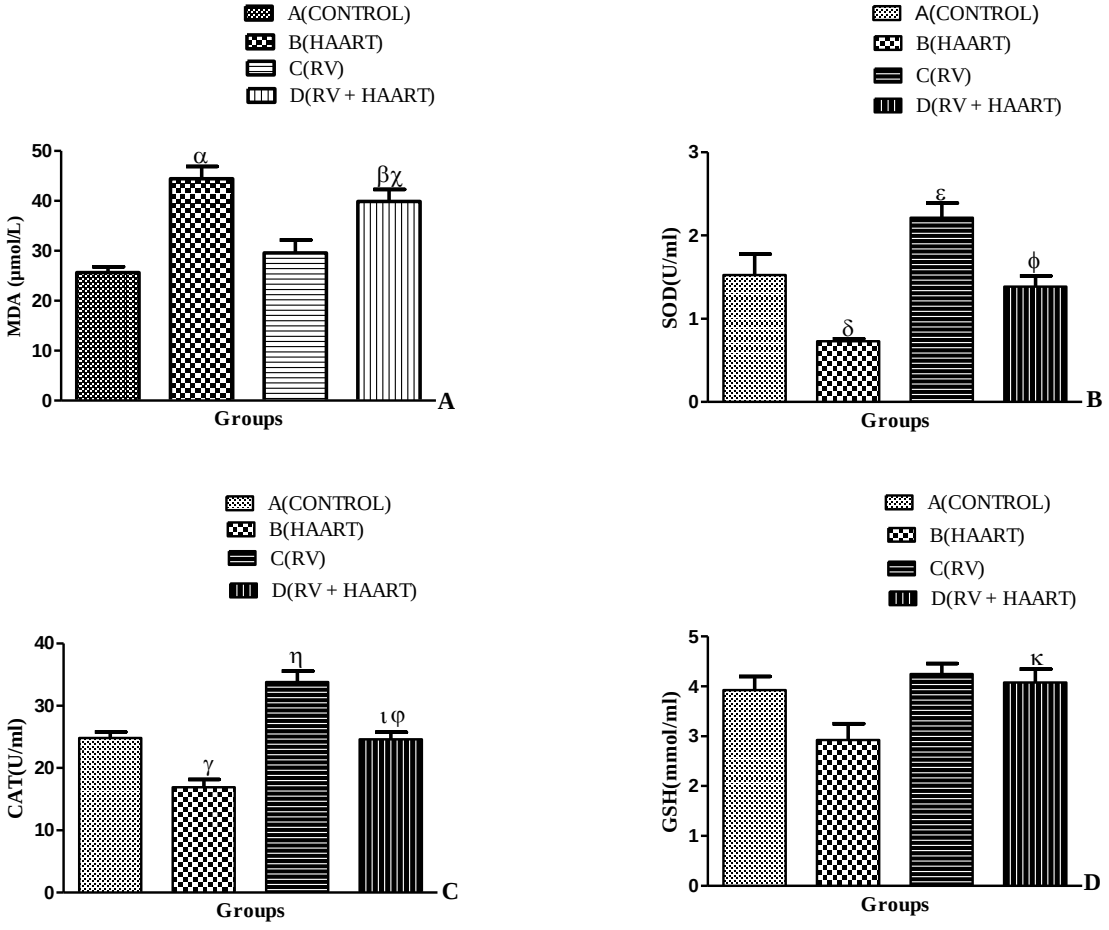

Figure 2: Effects of RV and HAART treatments on the Serum (I) malondialdehyde (MDA) (II) superoxide dismutase (SOD) (III) Catalase (CAT) and (IV) reduced glutathione (GSH) levels in Wistar rats after 6-week treatment period.
Bars indicate the mean ± SEM. A(Control); B(HAART), C (RV), D (RV+HAART). The comparison groups were B, C, D versus A; D versus B; and D versus C.
For MDA: [α]($p < 0.001$) B vs A; [β]($p < 0.01$) D vs A; [χ]($p < 0.01$) D vs C
For SOD: [δ]($p < 0.05$) B vs A, [ε]($p < 0.05$) C vs A; [Φ]($p < 0.05$) D vs C
For CAT: [γ]($p < 0.01$) B vs A, [η]($p < 0.001$) C vs A; [ι]($p < 0.01$) D vs B; [φ]($p < 0.01$) D vs C
For GSH: [κ]($p < 0.01$) D vs B

4. Discussion

Prolonged use of antiretroviral medications has been specifically associated with nephrotoxicity, as evidenced by several studies showing decreased renal function in individuals undergoing HAART (36, 37). The current study demonstrates the impact of HAART on renal cytoarchitectural patterns. Qualitative light microscopic analysis using H&E staining revealed interstitial inflammation, tubular atrophy, vacuolization, and deleterious cellular morphological changes, particularly characterized by a high prevalence of tubular granular degeneration. Our results are in agreement with previous studies by Offor, Naidu (28) and Kwizera, Ssekatawa (38), which indicated that the initiation of HAART induced a marked disruption in the cytoarchitectural configuration of the kidney, including glomerular capillaries irregularities, vacuolization, tubular necrosis, tubular epithelial desquamation, and extracellular matrix accumulation. This suggests that there may have been substantial changes leading to the disruption of glomerular capillaries and mesangial cells due to HAART administration (39). Resveratrol administration attenuated severe histopathological changes and promoted renal tubular regeneration. In addition, resveratrol exhibited a therapeutic effect on the kidney, as evidenced by the restoration of regular renal cell distribution in the resveratrol-only treatment group and progressive renal cell recovery in the combined resveratrol and HAART treatment group. This underscores the potential of resveratrol as a potent antioxidant in alleviating the negative effects of HAART and its connections, as suggested by current and previous research emphasizing its role in preventing the production of Reactive Oxygen Species (ROS) beyond physiologically safe thresholds (40).While no particular deficit in energy production pathways or structural irregularities were revealed by a mitochondrial DNA denaturation analysis, resveratrol could potentially enhance the observed structural changes by preventing pro-oxidants from deactivating antioxidant enzymes. This is consistent with previous research on the pro-oxidative effects of resveratrol (41). Glomerular irregularities typically reduce the surface area available for filtration, leading to a decrease in glomerular filtration rate and metabolic functions (42). Reductions in glomerular filtration rate can culminate in the accumulation of wastes and toxins in the circulatory system, causing electrolyte and fluid imbalances in the body (43). Elevated serum levels of renal electrolytes indicate a functional strain on the nephron, possibly induced by decreased glomerular filtration rate, increased tubular reabsorption, or increased ion excretion (44). A statistically significant increase in serum sodium and chloride concentrations was observed when comparing group B animals exposed to HAART with controls. These results are consistent with a previous study showing that HAART recipients had higher calcium, chloride, and sodium levels than controls (45). Similarly, a recent study by Kwizera, Ssekatawa (38) reported significantly higher levels of potassium, sodium, and chloride in HAART-treated rats than in control rats. Elevated levels of sodium and chloride in the bloodstream have been linked to failed renal function by interfering with the typical renal functio and causing disturbances in osmotic balance (46). Elevated blood sodium and chloride concentrations may alter the renal tubular osmolarity, leading to decreased efficiency of water reabsorption and waste elimination (47). Hypertonic sodium chloride infusions, resulting in excessive chloride exposure, have been correlated with hyperchloremia and acute kidney injury (AKI) in individuals with neurological trauma (48). However, a study on Traumatic Brain Injury (TBI) patients found no significant association between increased chloride intake from hypertonic saline solutions and AKI, suggesting no adverse effect on renal function (49). The induction of hyperchloremia by chloride-rich solutions has been proposed to trigger renal vasoconstriction and AKI (50), underscoring the need for further research to clarify the interplay between fluid composition, electrolyte levels, and renal failure. Therefore, the relationship between serum sodium, chloride levels, and renal injury is complex and context-dependent, although elevated serum chloride levels may indicate renal dysfunction in specific scenarios. Renal dysfunction is indicated by elevated blood urea nitrogen (BUN) and serum creatinine levels (51). Because BUN and creatinine are common waste byproducts excreted by the kidneys, elevated levels of these indicators indicate impaired renal function (52). In rats subjected to HAART, significant deterioration in renal function was observed along with markedly elevated BUN and serum creatinine levels. The significant increase in BUN and serum creatinine levels could potentially be attributed to the substantial percolation induced by tubular degeneration and glomerular hypercellularity. This is consistent with reports on the response to HAART treatment, indicating a robust correlation between elevated BUN, serum creatinine levels, and renal maladies linked to impaired renal function (38). The levels of renal injury markers (serum creatinine and BUN) showed a significant decrease after resveratrol treatment in group D, preventing the onset of nephrotoxicity. The mitigation of HAART-induced renal injury after resveratrol supplementation further supports the bioactive properties of resveratrol (53). Antiretroviral medications have been documented to induce a variety of potentially fatal consequences, most notably mitochondrial malfunction resulting from changed mitochondrial DNA (mtDNA) replication and the production of reactive oxygen species (ROS), which cause oxidative stress (54). The adverse effects of oxidative stress on renal function, leading to nephrotoxicity are well-recognized. The presence of renal insufficiency could suggest a simultaneous increase in oxidative mechanisms and a decrease in antioxidant protection (55). Lipid peroxidation, an adverse consequence of oxidative damage, free radical attack and excessive ROS formation, is a pivotal factor in the pathophysiological mechanisms of drug-induced nephrotoxicity (56). In the field of oxidative and redox stress signaling, Malondialdehyde (MDA) continues to serve as a relevant indicator to assess the level of lipid peroxidation (57). Our results showed elevated levels of MDA in the HAART-treated cohorts compared to the placebo and resveratrol groups, consistent with previous research indicating increased renal MDA levels after the antiretroviral drugs administration (58). Prolonged use of antiretroviral drugs is a key contributor to the increased production of reactive oxygen species (ROS), which triggers mitochondrial

dysfunction and promotes cellular aging and deterioration (59). The interference of HAART with the mitochondrial electron transport chain can negatively affcet ATP production and cellular respiration through complex inhibition I, which is associated with the development of degenerative kidney diseases (60). In addition, our findings supports previous studies indicating that HAART reduces cell proliferation by prolonging the duration of the cell cycle, increasing apoptosis, and gradually decreasing renal function (61, 62). GSH, CAT, and SOD serve as vital markers that reflect the body's antioxidant prowess. (63). They can show the rate of lipid peroxidation and body intensity as well as the extent of tissue oxidation (64). In this study, the activities of superoxide dismutase (SOD), glutathione (GSH), and catalase (CAT) were used assess the reaction of the kidney to oxidative damage induced by combined treatment with HAART and RV. The levels of SOD, GSH, and CAT were significantly decreased in the HAART group B and significantly increased in the groups receiving RV therapy concurrently. Furthermore, RV exerted its antioxidant effects on HAART-induced damage by eliminating free radicals and averting lipid peroxidation-mediated oxidative DNA damage in all treated groups. The substantial presence of RV phenolics suggests its efficacy as a potent antioxidant compound with favorable pharmacokinetic properties, helping to mitigate mitigating the detrimental effects of HAART and its potential connections. Oxidative stress, inflammation, and mitochondrial dysfunction induced by HAART play a critical role in the progression of renal impairment. Conversely, RV has been observed to interact with various signaling molecules, leading variety of therapeutic effects, including antioxidant and anti-inflammatory properties, which can mitigate nephrotoxicity and facilitate restoration of renal function (65). In addition, resveratrol exhibits protective properties against renal ischemia-reperfusion injury by reducing serum creatinine and blood urea nitrogen levels, mitigating oxidative stress, and increasing antioxidant enzyme activity (66). RV can potentially function as a renal-degeneration agent that inhibits apoptosis, restore renal loss, and repair damaged molecular targets (67). Nevertheless, our research highlighted the nephroprotective capacity of resveratrol in mitigating HAART-induced nephrotoxicity and restoring renal function. In conclusion, HAART has been instrumental in prolonging the lives of people infected with HIV/AIDS. However, it is crucial to recognize that HAART could potentially disrupt the consistency of drug use, thereby affecting the structural integrity and functional parameters of the kidneys. The antioxidant properties inherent in resveratrol have shown promise in ameliorating these adverse effects and improving renal function. It is imperative that further research efforts be undertaken to accurately quantify and understand the implications of these phenomena.

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Authors' Contribution
OOO conceived, designed, analyzed, supervised the experiment, and drafted the manuscript. IEO was involved in methodology and project management. AAO provided technical support for the study. ABO and AOA provided material support and reviewed the manuscript.

Ethics
Not applicable as no human study was conducted.

Conflict of Interest
We declare that there was no conflict of interest regarding the publication of this paper.

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Data Availability
The data that support the findings of this study are available on request from the corresponding author.

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