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Article

Resveratrol Mitigates Gold Nanoparticle-Induced Nephrotoxicity via Modulation of Oxidative Stress and Inflammation in Mice

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Abstract: Gold nanoparticles (AuNPs) hold promise for biomedical applications but raise safety concerns, particularly nephrotoxicity linked to oxidative stress, inflammation, and apoptosis. Resveratrol (RSV), a natural polyphenol with antioxidant and anti-inflammatory properties, may mitigate these adverse effects, yet its renoprotective role against AuNP-induced injury remains underexplored. Male mice (n = 30) were randomly assigned to three groups: control, AuNPs (8 mg/kg/day), and AuNPs + RSV (15 mg/kg/day). Treatments were administered orally for 14 days. Body and kidney weights were recorded, and renal tissues were analyzed for tumor necrosis factor-α (TNF-α), caspase-3, reduced glutathione (GSH), superoxide dismutase (SOD), and catalase (CAT). Data were analyzed using ANOVA with Tukey–Kramer post hoc testing. AuNP exposure significantly increased final body weight (30%) and relative kidney weight (92%) compared with controls ($P < 0.05$). RSV co-treatment prevented weight gain and attenuated kidney hypertrophy, reducing values to near-control levels. AuNPs markedly elevated renal TNF-α and caspase-3 activity, while RSV co-treatment normalized both markers. Similarly, AuNPs depleted renal GSH, SOD, and CAT, whereas RSV significantly restored these antioxidant defenses, though not fully to control levels. Histopathological analysis confirmed severe glomerular and tubular injury in the AuNP group, which was markedly alleviated by RSV pretreatment. AuNPs induce renal hypertrophy, oxidative stress, inflammation, apoptosis, and structural damage in male mice. RSV co-treatment substantially mitigates these biochemical and histopathological alterations through antioxidant, anti-inflammatory, and anti-apoptotic mechanisms, supporting its potential as a protective adjuvant in nanomedicine.

Keywords: Antioxidants, Apoptosis, Caspase-3, Nanomedicine, TNF-α

Introduction

Nanoparticles (NPs), defined as materials with at least one dimension between 1–100 nm, possess unique physicochemical properties that support their use in biomedical applications such as drug delivery, imaging, and diagnostics [1]. Among metallic nanomaterials, gold nanoparticles (AuNPs) are

particularly attractive due to their stability, tunable surface plasmon resonance, and ease of surface modification, enabling applications in targeted drug delivery, cancer therapy, and biosensing [2], [3].

Despite these advantages, concerns remain regarding their safety, especially nephrotoxicity. The kidneys play a central role in NP clearance, and particle size strongly influences biodistribution and toxicity. Small AuNPs (10–13 nm) readily accumulate in renal tissues, elevate reactive oxygen species (ROS), impair mitochondrial function, and induce apoptosis, whereas larger particles are generally less harmful [4], [5]. These nephrotoxic effects are closely linked to oxidative stress, inflammation, and tubular injury [6].

Resveratrol (RSV), a polyphenolic compound abundant in grapes, has well-documented antioxidant, anti-inflammatory, and anti-apoptotic properties. Mechanistically, RSV scavenges free radicals, inhibits lipid peroxidation, activates the Nrf2 pathway, and enhances endogenous antioxidant enzymes including SOD, CAT, and glutathione peroxidase [7]. It also protects against renal injury in models of ischemia–reperfusion, diabetic nephropathy, and toxin-induced damage [8], [9]. However, its clinical application is constrained by poor bioavailability [10]. Notably, RSV-functionalized AuNPs display stronger antioxidant effects than free RSV, suggesting a synergistic potential to enhance therapeutic efficacy while reducing toxicity [11], [12].

Although AuNPs hold promise in nanomedicine, their nephrotoxicity remains a critical barrier. RSV's unique antioxidant and anti-inflammatory activities make it a compelling candidate for mitigating NP-induced renal damage. To address this gap, the present study evaluated the nephroprotective role of RSV in male mice exposed to AuNPs, focusing on oxidative stress, inflammation, and apoptosis. The findings may inform safer strategies for integrating AuNPs into biomedical applications.

Materials and Methods

Chemicals

AuNPs (15 ± 5 nm) and RSV were purchased from Nano Gate Company (Cairo, Egypt). RSV was dissolved in dimethyl sulfoxide (DMSO) and diluted with ethanol to obtain a final concentration of 2% DMSO before administration. Enzyme-linked immunosorbent assay (ELISA) kits for mouse tumor necrosis factor-α (TNF-α; Cat# SL0547Mo) and caspase-3 (Cat# SL0679Mo) were obtained from Sun-Long Biotech Co. (China). Kits for GSH (Cat# BC1175), SOD; (Cat# BC0175), and CAT were purchased from Solarbio Co. (Beijing, China). The size, morphology, and purity of AuNPs were verified prior to use by transmission electron microscopy and UV–Vis spectrophotometry, which confirmed the manufacturer's specifications [13].

Animals and Experimental Design

Adult male mice weighing 24 ± 3 g were obtained from the Drug Control Center in Baghdad and housed at the College of Veterinary Medicine, University of Fallujah. The animals were kept under standard laboratory conditions with free access to food and water and were allowed to acclimatize for two weeks prior to experimentation. A total of thirty mice were randomly divided into three groups of ten. The first group served as the control and received vehicle only. The second group was administered AuNPs at a dose of 8 mg/kg/day by oral gavage for 14 days [13], [14]. The third group was given the same AuNP dose in combination with RSV at 15 mg/kg/day for 14 days [15]. All experimental procedures were approved by the Institutional Ethics Committee of the Faculty of Veterinary Medicine, University of Fallujah (UOF.VET.2024.001), and were conducted in accordance with the Guide for the Care and Use of Laboratory Animals.

During both the acclimatization and treatment periods, all mice were carefully observed for any clinical signs of toxicity, including body weight changes by 10% or more, behavioral changes, stress responses, physical abnormalities, or mortality.

Tissue Collection and Kidney Homogenate Preparation

At the end of the treatment period, mice were anesthetized with isoflurane (2% inhalation) and sacrificed. The kidneys were immediately excised, rinsed in ice-cold 0.9% saline, and cleared of adherent connective tissue. Each kidney was homogenized (10% w/v) in ice-cold phosphate buffer (0.01

M, pH 7.4) containing 1.15% KCl using a mechanical homogenizer. The homogenates were centrifuged at 10,000 × g for 20 minutes at 4 °C, and the supernatants were collected and stored at –80 °C until further biochemical analyses.

Biochemical Assays in Kidney Tissues

Caspase-3 activity was measured in kidney homogenates using an Elabscience kit (Texas, USA), while TNF-α levels were determined with a Transgenbiotech kit (Beijing, China), following the manufacturers' instructions and previously reported methods [1], [14]. The GSH content was determined as described elsewhere [16]. SOD and CAT activities were assessed using Solarbio kits (Beijing, China), following the methods described elsewhere [17]**.**

Histopathological study

Kidney samples were collected and fixed in 10% neutral buffered formalin until processing. Tissues were then dehydrated, embedded in paraffin, and sectioned at 5 μm thickness. Sections were stained with hematoxylin and eosin (H&E) following the standard method as reported elsewhere [18], and examined under a light microscope. Histopathological scoring was performed by evaluating the kidney cortex in H&E-stained sections.

Statistical Analysis

All data were analyzed using SPSS version 18.1 (Chicago, IL, USA). Results are expressed as mean ± SD for ten animals per group. The normality of distributions was tested using the Shapiro–Wilk test, and homogeneity of variances was assessed with Levene's test. Group comparisons were performed using one-way analysis of variance (ANOVA) followed by Tukey–Kramer's post hoc test for multiple comparisons. All tests were two-tailed, and statistical significance was set at $P < 0.05$..

Results and Discussion

Effect of AuNPs and RSV on Body and Relative Kidney Weights

Initial body weights were comparable among groups (~22 g). After 14 days, mice treated with AuNPs showed a significant ($P < 0.05$) 30% increase in final body weight compared with controls, whereas co-treatment with RSV prevented this elevation and restored body weight to near-control values (Table 1). Relative kidney weight was also significantly increased in the AuNP group (92%), indicating renal hypertrophy. RSV co-treatment attenuated this effect, reducing relative kidney weight, although values remained elevated (~62%) compared with controls (Table 1).

Table 1. Body and Renal Weights of Male Mice Treated with Gold Nanoparticles (AuNPs) Alone or with Resveratrol (RSV).

	Control	AuNPs	AuNPs + RSV
I.B.W. (g)	21.8 ±0.8	22.0 ± 0.5	21.9 ± 1.0
% change		+0.9*	+0.5*
F.B.W. (g)	23 ± 1.4	29.9 ± 1.9[a]	23.6 ± 1.5[b]
% change		+30*	-21**
R.K.W. %	0.26 ± 0.02	0.50 ± 0.06[a]	0.42 ± 0.02[a,b]
% change		+92*	-16**

Data are expressed as means ± standard deviation (SD); n = 10. [a]Significantly different from control, [b]significantly different from AuNPs group. I.B.W.: Initial body weight, F.B.W.: Final body weight, R.K.W. Relative kidney weight. *: Calculated from the control, **: calculated from the AuNPs group.

These findings align with earlier reports that AuNP exposure can disrupt metabolic regulation and induce renal enlargement, with severity influenced by particle size, dosage, and exposure duration [19]**.** Such effects have been attributed to AuNP-mediated oxidative stress and inflammatory signaling,

which impair lipid metabolism and energy homeostasis [20]. Increased oxidative stress may also contribute to fluid retention and tissue remodeling, further explaining the observed hypertrophy.

The protective role of RSV likely reflects its pleiotropic actions. RSV has been shown to inhibit adipogenesis and improve mitochondrial oxidative phosphorylation, thereby counteracting AuNP-induced metabolic disturbances [21]. Its ability to suppress pro-inflammatory mediators and ROS may also contribute to the prevention of renal hypertrophy, as inflammation-driven tubular injury is a recognized outcome of AuNP accumulation. Although RSV reduced kidney weight substantially, complete normalization was not achieved, underscoring the complexity of AuNP-induced toxicity and possible limitations related to RSV bioavailability.

Together, these results suggest that AuNPs promote systemic metabolic dysregulation and renal remodeling through oxidative and inflammatory mechanisms, while RSV co-treatment substantially mitigates these adverse effects.

Effect of AuNPs and RSV on Inflammatory and Apoptosis Markers

To determine whether renal hypertrophy was accompanied by molecular signatures of injury, inflammatory and apoptotic markers were examined. AuNP administration markedly increased renal TNF-α levels (Fig. 1A) and caspase-3 activity (Fig. 1B) compared with controls ($P < 0.05$), confirming activation of inflammatory and apoptotic pathways. Co-treatment with RSV attenuated these elevations, restoring values close to those of the control group.

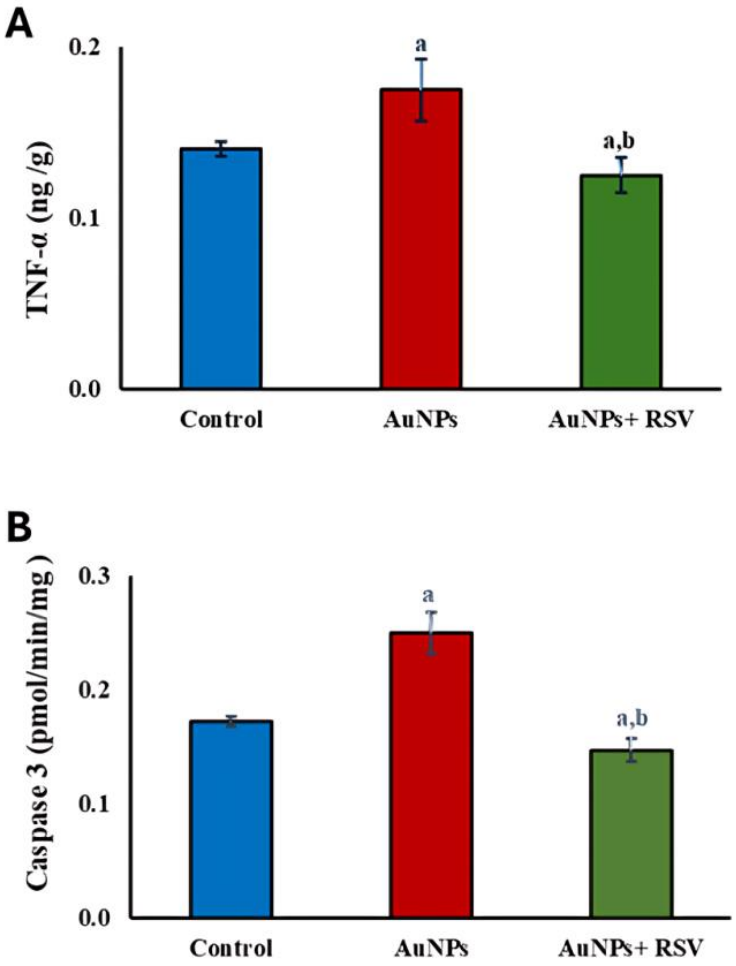

Figure 1. Effect of gold nanoparticles (AuNPs) and resveratrol (RSV) on renal A) Tumor necrosis factor-α (TNF-α) level, and B) Caspase-3 activity. Data are expressed as means ± standard deviation (SD); n = 10. [a]Significantly different compared with control, [b]significantly different compared with AuNPs group.

These findings agree with previous studies showing that AuNPs activate NF-κB signaling, a central pathway driving transcription of pro-inflammatory cytokines including TNF-α [22], [23]. Elevated TNF-α amplifies renal inflammation and contributes to apoptotic signaling through death receptor pathways. Caspase-3, a key executioner caspase, represents the final step of apoptosis, cleaving structural and regulatory proteins to dismantle the cell [24]. Its upregulation is therefore a hallmark of AuNP-induced apoptotic injury in renal tissue [25].

RSV's ability to reduce TNF-α levels and caspase-3 activity is consistent with its known effects on suppressing NF-κB activation, limiting pro-inflammatory cytokine release, and blocking apoptotic execution [25]. These results support a mechanistic model in which RSV protects against AuNP-induced renal damage through coordinated anti-inflammatory and anti-apoptotic actions.

Effect of AuNPs and RSV on Antioxidant Parameters

Because oxidative stress is a major driver of inflammation and apoptosis, renal antioxidant defenses were evaluated. AuNP-treated mice showed significant reductions in GSH content and in the activities of SOD and CAT compared with controls ($P < 0.05$) (Fig. 2A–C). Co-treatment with RSV significantly prevented these reductions, although full normalization to control levels was not achieved.

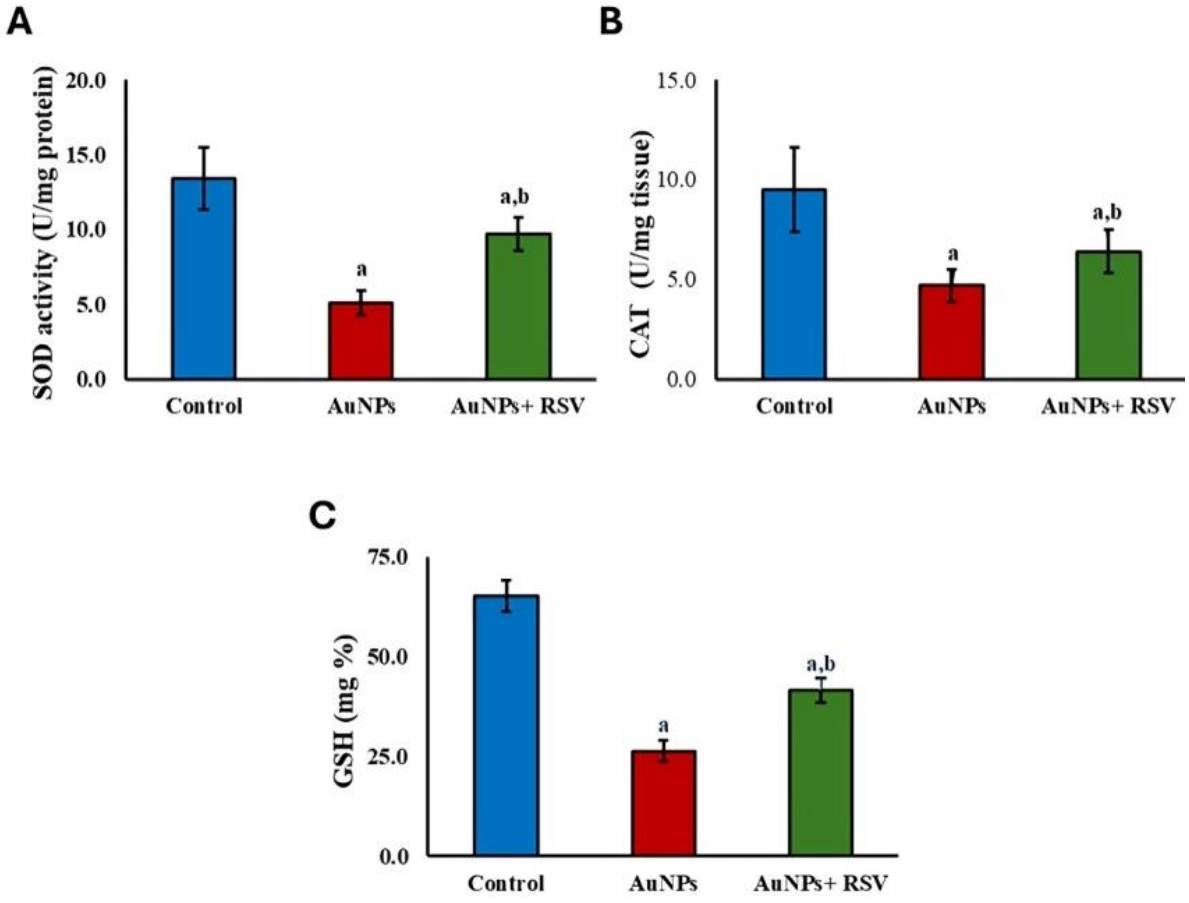

Figure 2. Effect of gold nanoparticles (AuNPs) and resveratrol (RSV) on renal A) Superoxide dismutase (SOD) activity, B) Catalase activity and C) Reduced glutathione (GSH) level. Data are expressed as means ± standard deviation (SD); n = 10. [a]Significantly different compared with control, [b]significantly different compared with AuNPs group.

The decline in antioxidant capacity following AuNP exposure is consistent with reports that nanoparticles elevate ROS, disrupt mitochondrial function, and suppress endogenous defense systems [26]. Each antioxidant marker plays a distinct role: GSH maintains redox balance as a major non-

enzymatic antioxidant, SOD catalyzes the dismutation of superoxide radicals into hydrogen peroxide, and CAT detoxifies hydrogen peroxide into water and oxygen. The simultaneous reduction of these defenses indicates a net oxidative burden imposed by AuNPs.

RSV's partial restoration of GSH, SOD, and CAT emphasizes its dual role as a direct free radical scavenger and as an activator of endogenous defense pathways, particularly through the Nrf2 antioxidant response [16]. Recent studies further confirm RSV's ability to attenuate nanoparticle-induced oxidative injury, both in its free form and when functionalized with AuNPs [27].

Importantly, these biochemical findings are consistent with the observed changes in TNF-α and caspase-3, since oxidative stress is a key upstream trigger of both inflammatory and apoptotic signaling cascades. This integrated response is also reflected in the structural changes observed histologically.

Effect of AuNPs and RSV on Kidney Histopathology

Histological examination provided morphological confirmation of the biochemical alterations. Kidney sections from the control group revealed normal architecture, with intact glomeruli, well-preserved renal tubules, and no evidence of degeneration, congestion, or inflammatory infiltration (Fig. 3A).

In contrast, kidneys from mice treated with AuNPs exhibited pronounced pathological alterations, including glomerular atrophy, acute tubular cell swelling, and interstitial hypercellularity (Fig. 3B). These features are consistent with oxidative damage to renal cells, inflammatory infiltration, and apoptotic remodeling—findings that parallel the biochemical elevations in ROS, TNF-α, and caspase-3. Inflammatory cell infiltration in renal tissue after GNP exposure, predominantly neutrophils and mononuclear cells was previously reported [22]. Such findings suggest that GNPs interact with renal proteins and enzymes, disrupting antioxidant defenses and enhancing ROS production, thereby eliciting inflammatory damage. Other studies further support the size-dependent toxicity of GNPs, with smaller nanoparticles provoking stronger immune responses due to their higher surface reactivity [28], [29], [30]. Our observation of glomerular congestion and capillary dilatation in animals exposed to 10 and 20 nm GNPs, but not to 50 nm particles, supports this size effect. Similar phenomena have been described by [31], who observed proliferation of Bowman's capsule epithelial cells with smaller GNPs. Collectively, these results underscore the nephrotoxic potential of AuNPs, particularly at smaller particle sizes.

Remarkably, pretreatment with RSV substantially ameliorated the AuNP-induced renal damage. Kidney sections from this group largely retained normal morphology, with preserved glomeruli and tubules. Only mild alterations, such as dilatation and congestion of blood vessels, were noted (Fig. 3C). These structural improvements mirror RSV's ability to restore antioxidant defenses and suppress inflammatory/apoptotic markers, highlighting consistency across biochemical and morphological endpoints. Our findings are in line with earlier studies showing that RSV reduces inflammatory infiltration, tubular dilatation, and edema in ischemia–reperfusion models [32], [33]. The beneficial effects of RSV are likely mediated by its strong antioxidant and anti-inflammatory properties, which counteract ROS generation and preserve renal structural integrity.

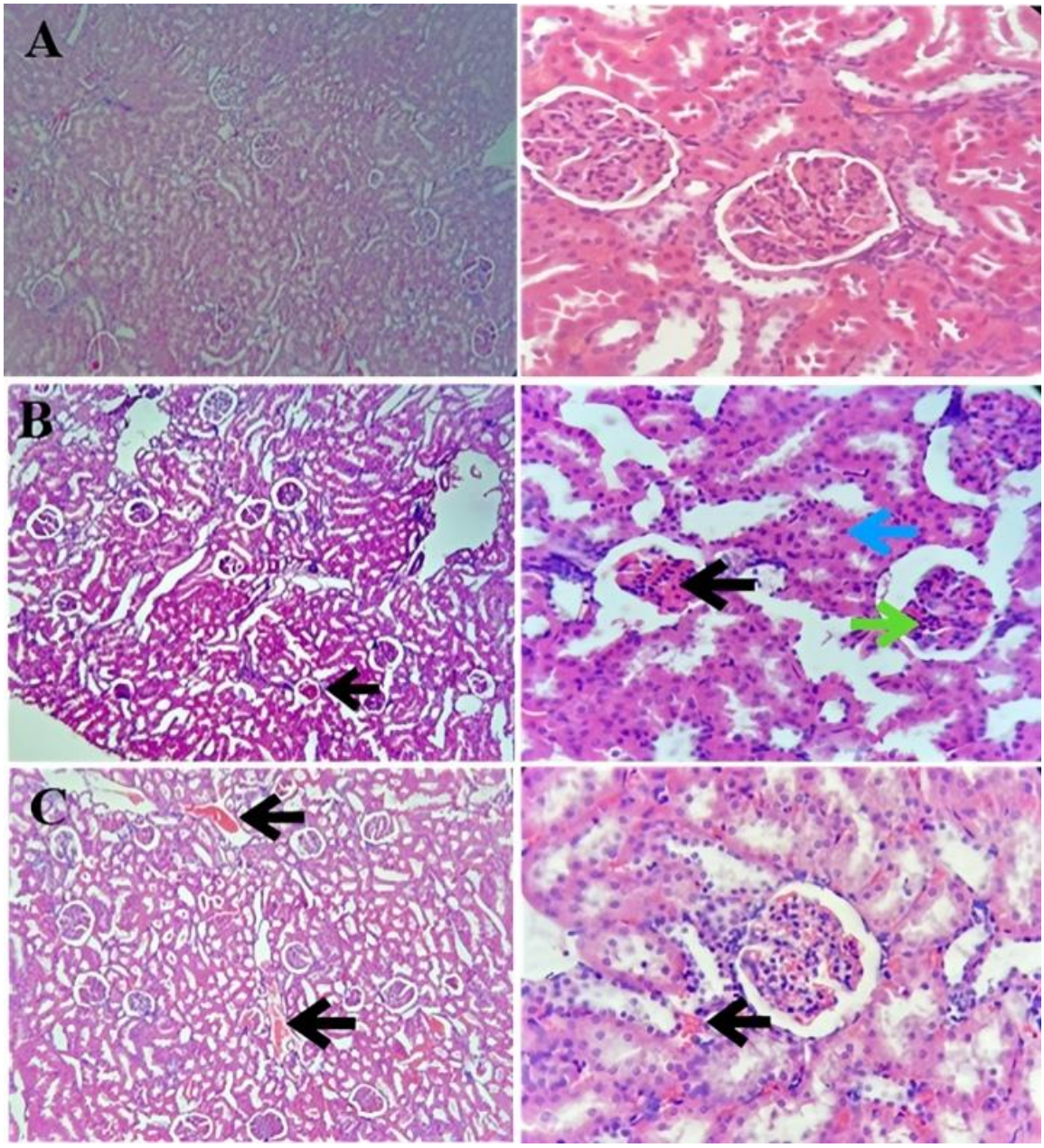

Figure 3. Representative photomicrographs of renal histology in mice. (A) Control group showing normal renal architecture with intact glomeruli and well-preserved tubules. (B) AuNP-treated group displaying marked pathological alterations, including glomerular atrophy, tubular cell swelling, and interstitial hypercellularity. (C) AuNP + RSV group exhibiting largely preserved renal morphology with only mild alterations, such as vascular dilatation and congestion. Hematoxylin and eosin (H&E) staining; images are shown at low magnification (×10, left) and high magnification (×40, right).

Study Limitations

This study provides important insights into the nephrotoxic effects of AuNPs and the protective role of RSV; however, several limitations should be acknowledged. First, only a single AuNP dose and exposure duration were tested, which may not fully capture dose–response relationships or chronic effects. Second, the study was conducted exclusively in male mice, and potential sex-related differences in nanoparticle toxicity or RSV response were not assessed. Finally, although RSV provided clear protective benefits, full normalization was not achieved. This may reflect limitations in its bioavailability, and future studies exploring optimized formulations or delivery approaches could further enhance its therapeutic potential.

Conclusion

This study demonstrates that gold nanoparticles (AuNPs) induce systemic and renal toxicity in male mice, evidenced by abnormal weight gain, renal hypertrophy, oxidative stress, inflammation, apoptosis, and marked histopathological deterioration of renal tissue, including glomerular atrophy, tubular cell swelling, and interstitial hypercellularity. Co-treatment with resveratrol markedly attenuated these adverse effects, restoring antioxidant defenses, suppressing inflammatory cytokines, reducing apoptotic activity, and preserving renal architecture with only mild vascular changes.

Although complete normalization was not achieved, RSV consistently provided substantial protection across functional, biochemical, and structural endpoints. These findings highlight RSV as a promising natural adjuvant to improve the safety of AuNP-based biomedical applications. By targeting oxidative stress and inflammatory pathways while preserving renal morphology, RSV supplementation may help minimize the nephrotoxic risks associated with nanomaterials, thereby supporting their safer translation into clinical practice.

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