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RESEARCH

Resveratrol regulates nickel oxide-induced kidney damage by targeting the PERK/ATF-6/IRE1 and Nrf2/HO1 pathways

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Abstract

Nickel oxide (NiO) is one of the most toxic heavy metals and poses a danger to human and animal health by causing serious kidney damage. Resveratrol (RES) is a flavonoid with antioxidant and anti-inflammatory properties, abundant in grapes and fruits. The current study is a first to investigate how RES affects oxidative stress, apoptosis, endoplasmic reticulum (ER) stress, inflammation, and histopathology against NiO-induced nephrotoxicity in rats using molecular, histological, immunohistochemical, and biochemical methods. The study used 24 Sprague–Dawley rats, randomly distributed into 4 groups of 6 rats each. The groups were designated as control, RES (10 mg/kg), NiO (10 mg/kg), and RES plus NiO. For 28 days, the prescribed doses of NiO and RES were given to the rats through gavage. After receiving NiO for 28 days, rats showed elevated levels of blood urea, creatinine, and uric acid. It has led to a rise in malondialdehyde (MDA) levels, an indicator of oxidative stress, and a decline in the transcription factor nuclear factor erythroid 2–related factor 2 (Nrf2) and antioxidant enzymes (HO-1, SOD, CAT, GPx, and GST). NiO application also increased the levels of IL-1β, TNF-α, 8-OHdG, and caspase-3 and the expression of endoplasmic reticulum (ER) stress markers such as heat shock proteins (HSP70, HSP90), GRP78, PERK, ATF6, ATF4, IRE1, XBP1, and CHOP, leading to histopathological changes in kidney tissues. RES administration significantly improved histological appearance by reducing impaired renal biochemistry, increased oxidative stress, inflammation, and ER stress. These results demonstrated that RES reduced NiO-induced nephrotoxicity.

Keywords Nickel oxide · Resveratrol · Oxidative stress · Endoplasmic reticulum stress · Apoptosis · Histopathology

Abbreviations

IL-1β	Interleukin 1 beta
SOD	Superoxide dismutase
CAT	Catalase
GPx	Glutathione peroxidase
GST	Glutathione s-transferase
HO-1	Heme oxygenase-1
8-OHdG	8-Hydroxy-2'-deoxyguanosine
TNF-α	Tumor necrosis factor–alpha
PERK	Protein kinase RNA-like ER kinase
ATF-6	Activating transcription factor 6
GRP78	78 KDa glucose-regulated protein
ATF-4	Activating transcription factor 4
IRE1	Inositol-requiring enzyme 1
CHOP	C/EBP homologous protein
XBP1	X-box binding protein 1

Introduction

Nickel oxide is a chemical compound with a crystal lattice structure (Joyner et al. 2024). Due to its chemical structure, it shows high thermal stability, electrical conductivity, and catalytic activity, and as a result, it sees a wide range of use (Joyner et al. 2024). Ceramics, batteries, and alloys are the primary contenders in terms of nickel oxide usage, while electronic devices and sensors follow suit; nearly all of which are in frequent use and direct contact and exposure with humans (Manna and Bandyopadhyay 2019). Consequently, there has been much research on how nickel oxide might affect human health for both micro- and nanoparticles (Adiguzel et al. 2023; Jeong et al. 2022; Wang et al. 2023; Yang et al. 2024; Dumala et al. 2019; Noshy et al. 2022). Microparticles are defined as particles smaller than 0.1 μm, and nanoparticles are defined

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as particles smaller than 100 nm in size (Noshy et al. 2022; Wieland et al. 2022). This difference in size, along with the shape, surface-to-volume ratio, and chemical activity, results in different mechanisms for toxicity in human cells (Adiguzel and Karaboduk 2024). Microparticles can produce important results in terms of histopathological effects on tissues and organs (Lyons-Darden et al. 2023). Although NiO microparticles are highly important in terms of accumulation and toxicological effects, the lack of an in-depth toxicity mechanism in the literature made this study necessary.

Nickel oxide exposure can occur through the gastrointestinal, pulmonary, or dermal routes (Lyons-Darden et al. 2023). In cases of exposure, it mixes with the blood and accumulates in organs, for instance, the liver and kidneys (Dumala et al. 2019). Previous research has indicated that exposure to NiO has adverse effects on renal tissue and, as a result, pathological processes such as tubular necrosis, interstitial inflammation, and glomerular congestion occur (Dumala et al. 2019). In another study in which NiO was administered orally, intraperitoneally, and intravenously, decreases in antioxidant enzyme activities and increases in apoptotic marker expression were observed, as well as significant pathological findings in the histomorphology of rat kidneys (Karaboduk et al. 2024a).

It has been established that nickel oxide leads to oxidative stress, genotoxicity, and inflammation (Adiguzel et al. 2023; Jeong et al. 2022; Wang et al. 2023; Yang et al. 2024; Dumala et al. 2019; Noshy et al. 2022). Reactive oxygen species (ROS), likes of which are hydrogen peroxide (H_2O_2), hydroxyl radicals (•OH), superoxide anions (O_2^-), and singlet oxygens (O_2), are highly reactive oxygen molecules which can be produced as a byproduct of metabolic activity, especially oxidative phosphorylation, and can even play a role in metabolism as a signaling molecule (Liu et al. 2023). When free radicals are present at excessive levels, they cause pathological damage by oxidizing DNA, lipids, and proteins (Liu et al. 2023).

Phenolics are secondary metabolites produced in response to stress in plants, with an emphasis on oxidative stress in plants (Duta-Bratu et al. 2023). Resveratrol is an antioxidant found mostly in grapes and fruits (Valletta et al. 2021; Duta-Bratu et al. 2023). It is a 14-carbon natural phenol with a C6–C2–C6 carbon structure, consisting of two benzene rings connected by an ethylene bridge, and it can exist in either cis or trans configuration (Valletta et al. 2021). It is known that it has anti-inflammatory, cardioprotective, and anticancer properties; increases the activity of antioxidant enzymes; and provides protection against lipid peroxidation (Diaz-Gerevini et al. 2016; Duta-Bratu et al. 2023). RES effectively cleans up hydroxyls, superoxides, and other radicals produced by metals thanks to its antioxidant properties. It acts as a metal chelator to protect cells from oxidative stress (Hafez et al. 2025). In a study where RES was used as an antioxidant, it was found that RES supplementation significantly improved liver toxicity and histopathological changes caused by silver particles administered to rats (Abdelrahman et al. 2022). In addition to its regulatory role in glucose and lipid metabolism, RES has healing properties on the cardiovascular system (Peng et al. 2025). RES is highly absorbed in humans when taken orally and is metabolized to sulfate conjugates in the liver and intestines and excreted in feces and urine (Yang et al. 2025a; Szymkowiak et al. 2025). The current study aims to investigate resveratrol's potential protective function against possible damage of NiO microparticles on renal tissue with many biochemical, histopathological and molecular parameters.

Materials and methods

Reagents

Resveratrol was purchased from BLDpharm (CAS No. 501–36-0), and nickel oxide (44 µm, 95% purity) was purchased from Nanogarific Nano Technology (CAS No. 1313–99-1).

Animals and experimental procedure

Animal experiments were conducted at Gazi University Laboratory Animal Breeding and Experimental Research Center. Twenty-four adult Sprague–Dawley rats (170–250 g) were obtained from this center. The animals were housed in special cages under standard laboratory conditions, with controlled temperature (20 ± 2 °C) and a 12-h light/12-h dark cycle. The rats had ad libitum access to standard food pellets and drinking water throughout the experiment. The animals to be used in the study are summarized in Table 1. Twenty-four animals were seperated into 4 groups, each group consisting of six ($n = 6$) animals, and administered via gavage once a day for 28 days.

In this study, the dose applied for NiO was selected based on the studies of Karaboduk et al. (2024a) and Singh et al. (2022a). The NiO dose to be applied for this study was determined as 10 mg/kg bw. Again, in this study, the

Table 1 Design of experimental

Groups	Treatment
Control group	1 ml/kg bw corn oil
RES group	10 mg/kg bw per day in corn oil
NiO group	10 mg/kg bw per day in distilled water
RES + NiO group	10 mg/kg bw per day in corn oil RES + 10 mg/kg bw per day in distilled water NiO

resveratrol application dose was selected based on the study conducted by Ibrahim et al. (2021) in the past, which showed that it provided protection against environmental pollutants.

After the tested substances were applied for 28 days, the experimental animals were dissected under anesthesia with the combination of ketamine + xylazine. Biochemical analyses were performed with blood samples taken from their hearts, and molecular, histopathological, and immunohistochemical studies were performed with kidney tissues isolated after dissection.

Body and organ weights

The weights of all animals in this study were recorded on the initial and final days of the 28-day application period, and after dissection, the kidney tissues were removed and weighed. The relative weights (%) of the kidney tissue were calculated as grams per 100 g of body weight.

Bioaccumulation of nickel in the kidney

For nickel determination under the conditions recommended by the manufacturer, a Varian (Palo Alto, CA, USA) AA240FS flame atomic absorption spectrometer equipped with a deuterium lamp background corrector, a nickel hollow cathode lamp (Varian), and an atomizer using an air-acetylene flame was used. 0.3-g kidney tissue samples were digested in 3 ml nitric acid, mixed with H_2O_2, and then diluted to 10 ml with ultrapure water. The wavelength, lamp current, slit width, and acetylene flow rate for Ni were 232.0 nm, 4 mA, 0.2 nm, and 2 l min^{-1}, respectively. Calibration standard solutions (1, 2, 4, and 8 mg/l^{-1}) were prepared by diluting a nickel stock solution (Merck Darmstadt, Germany) with a concentration of 1000 mg/l^{-1}. Calibration curves and equations were obtained by measuring the absorbance values of the element according to the concentrations of the working standard solutions (Yalçınkaya and Erdoğan 2012).

Renal function tests

Serum urea, creatinine, and uric acid levels were analyzed for renal function. Urea (Otto Scientific, OttoBC157), uric acid (Otto Scientific, OttoBC158), and creatinine (Otto Scientific, OttoBC139) were analyzed colorometrically on the Mindray-BS400 automatic analyzer utilizing commercial kits.

Analysis of oxidative stress parameters in renal tissues

For the analysis of oxidative stress parameters, renal tissues were homogenized with KCl and centrifuged at + 4 °C for 15 min. Protein levels in renal tissues were analyzed according to the method of Lowry et al. (1951). Malondialdehyde (MDA), superoxide dismutase (SOD), catalase (CAT), glutathione peroxidase (GPx), glutathione s-transferase (GST), nuclear factor erythroid 2 (Nrf2), heme oxygenase-1 (HO-1), 8-hydroxy-2'-deoxyguanosine (8-OHdG), and interleukin 1-Beta (IL-1β) were measured using the upper fluids of the homogenized tissues. The MDA level was measured by the method of Ohkawa et al. (1979), SOD activity by the method of Marklund and Marklund (1974), CAT activity by the method developed by Aebi (1984), GPx activity by the method of Paglia and Valentine (1987), and GST activity by the method developed by Habig et al. (1974). Nrf2 (BT-Lab, Cat No: E1083Ra), HO-1 (Elabscience, Cat No: E-EL-R0488), 8-OHdG (Elabscience, Cat No: E-EL-0028), and IL-1β levels (BT-Lab, Cat No: E0119Ra) were analyzed in a microplate reader by the ELISA method using commercial kits according to the manufacturer's instructions.

Quantitative real-time PCR analysis in renal tissues

The mRNA transcript levels of Protein Kinase RNA-Like ER Kinase (PERK), Activating Transcription Factor 6 (ATF-6), Activating Transcription Factor 4 (ATF-4), Inositol-Requiring Enzyme 1 (IRE1), C/EBP homologous protein (CHOP), and X-box binding protein 1 (XBP1) genes in kidney tissue were analyzed using the RT-PCR method. Primer sequences are presented in Table 2. Total RNAs were obtained from kidney tissue using a total RNA extraction kit (Invitrogen, Cat No: 15596026) and converted into cDNAs using the Otto synthesis kit (Otto Scientific, OttoP1152, Ankara). The obtained cDNAs were reacted with PERK, ATF-6, ATF-4, CHOP, XBP1, IRE1, and Actin-beta (Actb) as a housekeeping gene by the qRT-PCR method. The expressions of the relevant genes were measured by calculating the obtained data with the delta delta Ct (2-ΔΔCt) method (Livak and Schmittgen 2001).

Immunohistochemistry

HSP70 (Affinity, AF5466), HSP90 (Affinity, AF5368), GRP78 (Affinity, AF5366), TNF-α (Bioss, Bs-10802R), and caspase-3 (Bioss, Bs-2593R) were performed according to the procedures described by Adiguzel et al. (2025). Kidney sections of 5–6-µm thickness were passed through an increasing alcohol series. As a subsequent procedure, citrate buffer solution was applied for antigen retrieval. Sections were treated with 3% hydrogen peroxide for 15 min to mask endogenous peroxide. In the next step, 1/100 diluted antibodies were dropped onto the sections 15 min after UV serum block was dropped and kept at + 4 °C for 1 day. The secondary antibody HRP-streptavidin was then dropped onto the tissues and washed with PBS. Sections were then treated with DAB (3,3′-diaminobenzidine)

Table 2 Primer sequences

Gene	Sequences (5′−3′)	Length (bp)	Accession nos
PERK	F: GCGGCAGGTCCTTAGTAATC R: ACCAGATCCCACGTCCAAAT	104	NM_031599.2
ATF-6	F: CCAAAGGTCAGACTGTTTTGC R: ACACAGTTTTCCGTTCACCG	179	NM_001107196.1
ATF-4	F: ACCATGGCGTATTAGAGGCAG R: GTTTCGTGAAGAGCGCCA	121	NM_024403.2
IRE1	F: TGGACGGACAGAATACACCA R: TGTAGTCCACGTCATCCTCG	113	NM_001191926.1
CHOP	F: TCTTCATACACCACCACACCTG R: AGGGATGCAGGGTCAAGAGT	228	NM_001109986.1
XBP1	F: CATTCTGGACAAGTTGGACC R: TGATGAGGTCCCCACTGACA	81	NM_001271731.1
β-Actin	F: ACAACCTTCTTGCAGCTCCTC R: CTGACCCATACCCACCATCAC	200	NM_031144.3

chromogen and counterstained with Gill hematoxylin. To evaluate the immunoreactivity of HSP70, HSP90, GRP78, TNF-α, and caspase-3 antibodies, experimental groups were evaluated and their photographs were taken. A total of 100 measurements were taken from the experimental groups for each antibody. The measurements were analyzed in terms of immunoreactivity intensity with the Image J (1.53 k, National Institute of Health, USA) program. Then, statistical comparisons were made between the experimental groups.

Histopathological analysis

Post-experimentation, renal samples were acquired and subjected to fixation in 10% neutral formalin. In the next stage, an increasing alcohol series, xylol, and paraffin processes were carried out. Five- to six-µm-thick sections were taken from the tissues that were turned into paraffin blocks with a microtome. A routine hematoxylin and eosin (H&E) staining procedure was applied, and permanent preparations were made. Photographs were taken from the prepared preparations using an Olympus BX-51 light microscope and an Olympus EP50 camera integrated into the microscope. In view of the morphological changes, the following criteria were used for histopathological evaluation. Inflammatory cell infiltration, hemorrhage, glomerular degeneration, tubular degeneration, and edema were observed in kidney tissue. The degree of renal damage was classified on a scale of 0–5 and scored as 0 = none, 1 = 0–20%, 2 = 21–40%, 3 = 41–60%, 4 = 61–80%, and 5 = 81–100% involvement (Akin et al. 2025). All sections in the study group were examined, and the quantitative data obtained were compared statistically.

Statistical analyses

GraphPad Prism (GraphPad Software, La Jolla, California, USA) version 10 was used for statistical analyses. Shapiro–Wilk test was used to determine whether the data were normally distributed. For normally distributed data, one-way analysis of variance (ANOVA) and Tukey's post hoc test were used for intergroup significance test. For non-normally distributed data, Kruskal–Wallis test and Dunn's multiple comparison test were used to determine significance between groups. $p < 0.05$ was considered statistically significant.

Results

Body and organ weights

Table 3 shows the body and kidney weights of the rats. No significant difference in body weight was observed between the control group rats and the RES group rats ($p < 0.05$). However, a significant difference was detected in weight gain between the NiO group rats and the rats in the group where RES + NiO was administered together, compared to the control group rats ($p < 0.05$). However, no significant difference was observed between the NiO group and the RES + NiO group ($p < 0.05$). When evaluated in terms of kidney weights, no significant difference was observed between the control group and the NiO and RES + NiO groups of rats ($p < 0.05$).

Bioaccumulation of nickel

Figure 1 shows the level of nickel accumulated in the kidney tissues of all experimental groups. Compared to the control and RES groups, significant nickel accumulation was detected in the kidney tissue of rats in the NiO-treated group ($p < 0.05$). A significant decrease in nickel accumulation was observed in the kidney tissue of rats in the RES + NiO-treated group compared to the nickel accumulation in the NiO-treated group ($p < 0.05$).

Table 3 Effects of NiO and RES on the body and organ weights in rats

Parameters	Groups			
	Control	RES	NiO	RES + NiO
Body weight initial (g)	175.35 ± 5.75[a]	189 ± 12.81[a]	244 ± 15.17[a]	243 ± 18.67[a]
Body weight final (g)	241 ± 10.24[a]	252.5 ± 13.05[a]	265.2 ± 18.38[a]	277.8 ± 17.84[a]
Body weight change (%)	37.51 ± 5.77[a]	33.64 ± 4.02[a]	8.63 ± 1.39[b]	14.43 ± 1.86[b]
Absolute right kidney weight (g)	1.27 ± 0.08[a]	1.26 ± 0.11[a]	1.28 ± 0.11[a]	1.25 ± 0.1[a]
Relative right kidney weight (g)	0.5 ± 0.01[a]	0.5 ± 0.03[a]	0.48 ± 0.04[a]	0.45 ± 0.03[a]
Absolute left kidney weight (g)	1.26 ± 0.11[a]	1.24 ± 0.1[a]	1.3 ± 0.08[a]	1.27 ± 0.05[a]
Relative left kidney weight (g)	0.5 ± 0.01[a]	0.49 ± 0.02[a]	0.49 ± 0.04[a]	0.46 ± 0.02[a]

Results are given as mean ± SD ($n = 6$). Results are accepted as statistically significant when the $p < 0.05$. Different letters given as superscripts in each row indicate significance between groups

Renal function markers

As shown in Table 4, the urea, creatinine, and uric acid levels in the group of rats treated with NiO showed a significant increase compared to the control group ($p < 0.05$). It was found that resveratrol administered together with nickel oxide significantly reduced the urea, creatinine, and uric acid levels in the group of rats treated with nickel oxide alone ($p < 0.05$).

Oxidative stress parameters

After administering NiO and RES to rats in the study, the MDA level, which is the end product of lipid peroxidation, was evaluated, and the obtained data are shown in Fig. 2. Compared to the control group, renal MDA levels were significantly elevated in the NiO-treated group ($p < 0.05$). In contrast, no significant difference was detected between the control and RES groups. RES treatment significantly reduced the NiO-induced increase in MDA, bringing it closer to the control group values ($p < 0.05$).

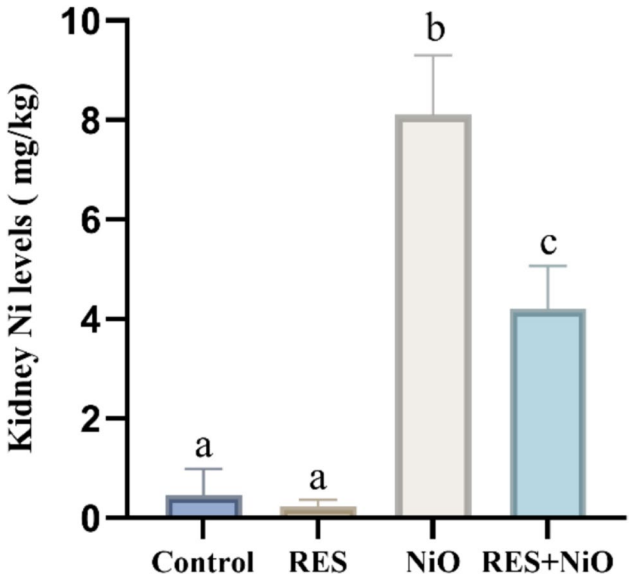


Fig. 1 Measurement of nickel levels and statistical analysis between experimental groups. Results are given as mean ± SD ($n = 6$). Results are accepted as statistically significant when the $p < 0.05$. Different letters given as superscripts in each row indicate significance between groups

The Nrf2 level regulating the expression of antioxidant activities and HO-1 enzyme activity is shown in Fig. 3. In the NiO-treated group, the Nrf2 level and HO-1 activity were significantly reduced compared to the control group ($p < 0.05$). In the group where RES and NiO were applied together, a significant increase in Nrf2 and HO-1 levels was detected (Fig. 3) ($p < 0.05$).

When renal tissue was evaluated for SOD, CAT, GPx, and GST antioxidant activities, a significant decrease was observed in the NiO-treated group compared to the control group ($p < 0.05$) (Fig. 4). RES supplementation, on the other hand, resulted in a significant increase in the parameters studied ($p < 0.05$) (Fig. 4).

The IL-1β level in renal tissue was significantly elevated in the NiO-treated group compared to the control group ($p < 0.05$), while the inflammation level increased by RES supplementation decreased ($p < 0.05$) (Fig. 5). The level of 8-OHdG, which is frequently used to indicate oxidative DNA damage, was investigated in kidney tissues, and a significant increase was observed in the NiO-treated group compared to the control group ($p < 0.05$). In the group treated with NiO together with RES, the 8-OHdG level decreased dramatically ($p < 0.05$) (Fig. 6).

Real-time PCR assessment

The relative mRNA transcription levels of PERK, ATF-6, ATF-4, IRE1, XBP1, and CHOP, genes, which are important markers of ER stress in renal tissue, are presented in Fig. 7. NiO application upregulated the mRNA transcription levels of PERK, ATF-6, ATF-4, IRE1, XBP1, and CHOP in renal tissue ($p < 0.05$). On the other hand, RES application dramatically reduced the endoplasmic reticulum stress markers induced by NiO application ($p < 0.05$) (Fig. 7).

Table 4 Effects of NiO and RES on renal function parameters of rats

Parameters	Groups			
	Control	RES	NiO	RES + NiO
Creatinine (mg/dl)	0.67 ± 0.03^{a}	0.66 ± 0.01^{a}	0.77 ± 0.01^{b}	0.73 ± 0.01^{c}
Urea (mg/dl)	24.13 ± 0.82^{a}	23.29 ± 0.73^{a}	33.07 ± 0.82^{b}	28.76 ± 0.67^{c}
Uric acid (mg/dl)	1.53 ± 0.03^{a}	1.52 ± 0.05^{a}	1.91 ± 0.04^{b}	1.71 ± 0.04^{c}

Results are given as mean ± SD ($n = 6$). Results are accepted as statistically significant when the $p < 0.05$. Different letters given as superscripts in each row indicate significance between groups

Immunohistochemical assessment

To evaluate changes in the expression of caspase-3, TNF-α, HSP70, HSP90, and GRP78 expression levels were evaluated using immunohistochemical staining, and the number of positive cells for caspase-3, TNF-α, HSP70, HSP90, and GRP78 expression was significantly increased in the NiO-treated group compared to the control group (Fig. 8). In the group treated with NiO together with RES, the number of immunopositive cells decreased significantly compared to the NiO-treated group (Fig. 8). The intergroup immunoreactivity evaluation of the parameters examined in the kidney tissue is shown in Fig. 9 ($p < 0.05$).

Histological assessment

The glomerular and tubular structures in the kidney tissues of the control group and resveratrol group rats exhibit a normal histological appearance (Fig. 10A and B). In the NiO group, pathological lesions such as glomerular degeneration, tubular degeneration, hemorrhage, mononuclear cell infiltration, and edema were observed (Fig. 10C and D). In the RES + NiO group, the observed pathologies were milder than those in the NiO group, with hemorrhage and mononuclear cell infiltration observed (Fig. 10E). The histological scoring table of kidney tissue is given in Fig. 10F.

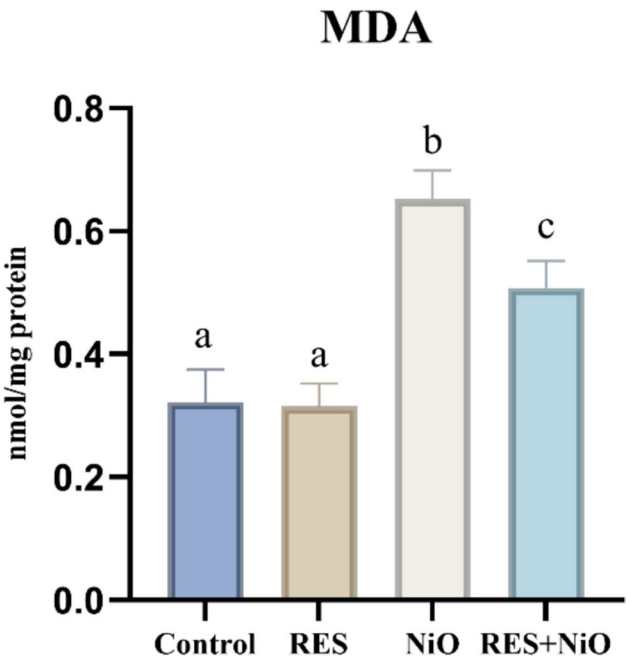


Fig. 2 Measurement of MDA levels and statistical analysis between experimental groups. Results are given as mean ± SD ($n = 6$). Results are accepted as statistically significant when the $p < 0.05$. Different letters given as superscripts in each row indicate significance between groups

Discussion

Toxicological studies show that renal toxicity causes direct tissue damage, inflammation, disruption of renal function, and changes in blood circulation (Al-Naimi et al. 2019). Among the basic functions of the kidney, plasma infiltration plays a crucial role in the secretion of erythropoietin and renin hormones, fluid homeostasis, and excretion of end products, but xenobiotics can impair the functioning of the kidney by disrupting the physiology and morphology of the kidney tissue (Rana 2021; Alhazmi et al. 2024). In the last few years, it has been known that exposure to heavy metals such as nickel leads to major health problems and that it is important to elucidate the mechanism underlying this toxicity (Hassanen et al. 2025). The LD_{50} dose of nickel oxide has been reported to be higher than 11,000 mg/kg in previous studies, and we would like to point out that the dose used in the current study is well below the LD_{50} dose (Henderson et al. 2012). Kidney tissue, which is very sensitive to particle toxicity along with its importance in the excretion of substances, is an organ where nickel metal accumulates (Abdulqadir and Aziz 2019a; Rana 2021). Resveratrol is a natural antioxidant and is an effective scavenger for radicals produced by lipid peroxidation, hydroxyls, and superoxide in cells (Hafez et al. 2025). In addition to scavenging free radicals, various studies suggest that resveratrol (RES) exhibits antioxidant effects not only directly through free radical scavenging but also through metal chelation. Due to its hydroxyl group, it coordinates redox-active ions such as Fe^{2+} and Cu^{2+}, limiting their participation in Fenton-type reactions and reducing the formation of reactive oxygen species (Belguendouz et al. 1997; Dias and Nikolaou 2011; Zeng et al. 2024). As a result, it acts as a powerful

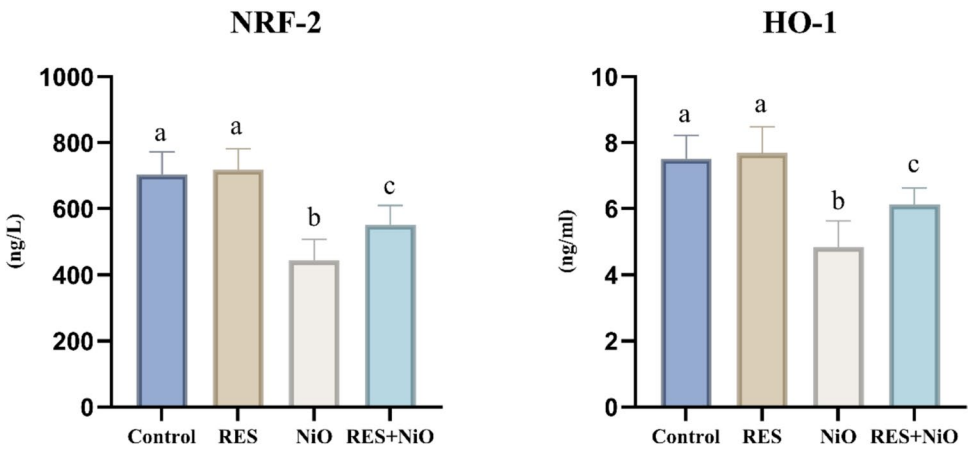


Fig. 3 Measurement of Nrf2 and HO-1 levels and statistical analyses between experimental groups. Results are given as mean ± SD ($n = 6$). Results are accepted as statistically significant when the $p < 0.05$. Different letters given as superscripts in each row indicate significance between groups

metal chelator, enzyme regulator, and radical scavenger (de Oliveira et al. 2021).

Monitoring changes in body weights and organ weights is one of the important parameters in toxicological studies (Karaboduk et al. 2024b). In previous studies using nickel oxide, it was reported that there was a decrease in weight gain in rats (Singh et al. 2021, 2022a). In the current study, it was observed that NiO-treated rats had decreased weight gain, while RES supplementation caused weight gain. However, no change was observed in organ weights.

Dose-dependent metal accumulation in organs has been shown in many studies (Dumala et al. 2019; Ali et al. 2021). Similarly, repeated dose rat studies have shown that nickel accumulations translocate to organs such as the liver, kidney and testes via the gastrointestinal system, resulting in histopathological, biochemical, and cellular damage (Ali et al. 2021; Singh et al. 2021, 2022a). In the current study, it was observed that the nickel accumulation in the NiO-applied group increased significantly compared to the control and resveratrol groups, while it decreased significantly in the

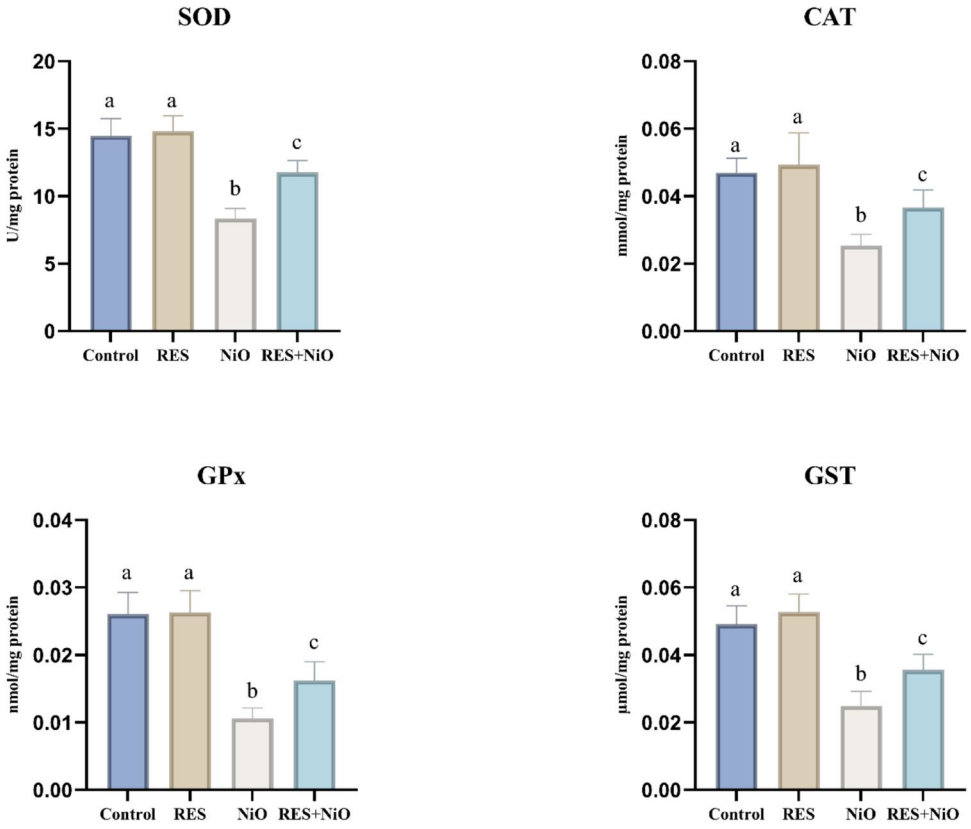


Fig. 4 Measurement of SOD, CAT, GPx, and GST activities and statistical analysis between experimental groups. Results are given as mean ± SD ($n = 6$). Results are accepted as statistically significant when the $p < 0.05$. Different letters given as superscripts in each row indicate significance between groups

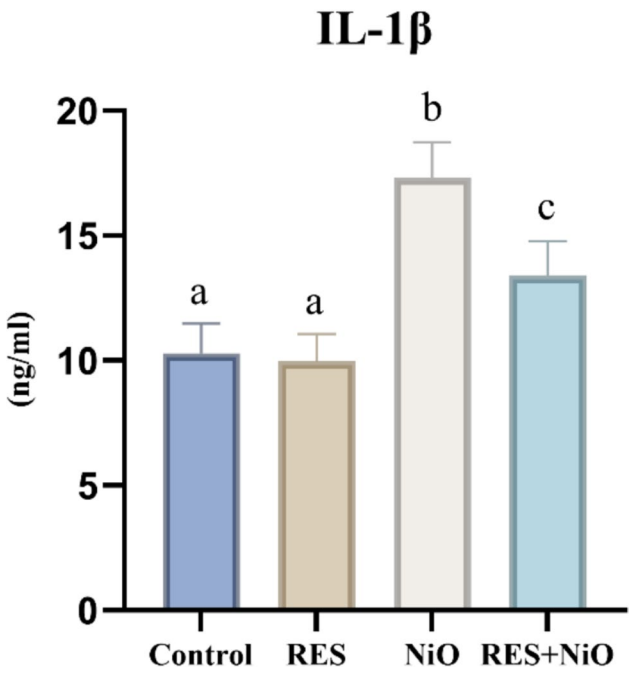


Fig. 5 Measurement of IL-1β levels and statistical analysis between experimental groups. Results are given as mean ± SD ($n = 6$). Results are accepted as statistically significant when the $p < 0.05$. Different letters given as superscripts in each row indicate significance between groups

resveratrol-nickel-applied group. This may be attributed to the chelating property of resveratrol.

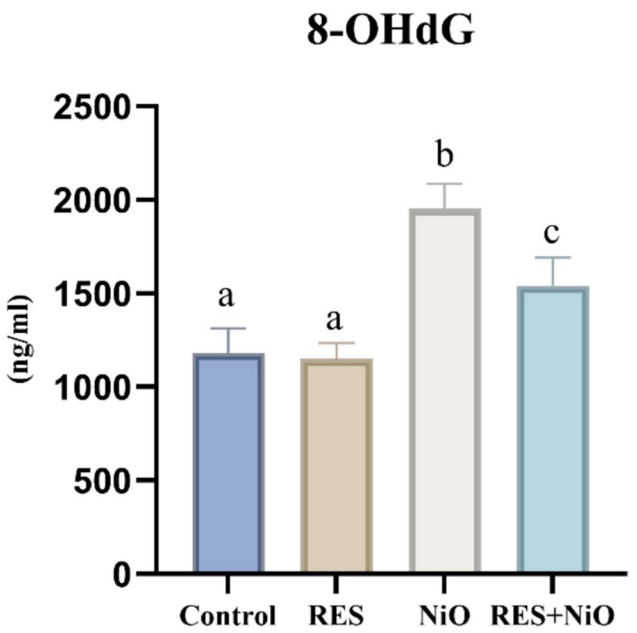


Fig. 6 Measurement of 8-OHdG levels and statistical analysis between experimental groups. Results are given as mean ± SD ($n = 6$). Results are accepted as statistically significant when the $p < 0.05$. Different letters given as superscripts in each row indicate significance between groups

The concentration of creatine, urea, and uric acid serves as key biomarkers for assessing renal functional capacity. Changes in their levels during their excretion in the kidney are indicators of renal diseases and have always been important parameters used to measure kidney functions (Adiguzel and Kalender 2020). It has been reported in earlier research that nickel increases creatinine, urea, and uric acid levels in rat kidneys (Abdulqadir and Aziz 2019b; Ali et al. 2021; Singh et al. 2022b). In the current study, it was observed that NiO application increases these parameters. This can be attributed to the accumulation of nickel in the kidney tissue and the deterioration of the filtration structure (Dumala et al. 2018). Likewise, the histological changes observed in the current study support this situation. It has been observed that RES application is effective in reducing renal damage and reduces urea, creatinine, and uric acid levels. Similarly, Hu et al. (2017) reported that heavy metal application in rats increased urea and creatinine values in kidney tissue, while RES application alleviated kidney damage and approached normal values.

Excessive ROS increases lead to a decline in antioxidant capacity, causing oxidative stress, which in turn leads to progressive oxidative damage and tissue injury (Uzunhisarcikli et al. 2023). The ROS-induced toxic mechanism of nickel is shown in (Fig. 11). Oxidative stress is a direct contributor to the pathogenesis of numerous diseases. It elevates lipid peroxidation by directly targeting lipids, a primary constituent of the cell membrane (Kalender et al. 2019; Kankılıç et al. 2024). MDA, the final product of lipid peroxidation, is formed by the peroxidation of unsaturated fatty acids in the cell membrane and is shown to be an indirect indicator of tissue and organ damage (Adiguzel et al. 2024). Previous studies suggest that metallic nickel increases MDA levels by increasing ROS in tissues depending on the dose and duration (Singh et al. 2022b; Karaboduk et al. 2024a). In this study, MDA levels were found to have significantly increased in the renal tissue of the NiO group. This suggests that this is a result of lipid peroxidation caused by an increase in reactive oxygen species (ROS) in the kidney tissue of the NiO group. RES application significantly reduced the increase in LPO. RES, as a natural metal chelator, may protect cell membranes from lipid peroxidation with its hydroxyl, superoxide, and nitric oxide scavenging properties (AlBasher et al. 2020). Previous studies also suggest that RES reduces MDA levels (Hafez et al. 2025; Elewa et al. 2025).

Nrf2 is a primary transcription factor activated by excessive oxidative stress and used in many redox reactions (Akarsu et al. 2024). In addition to regulating the physiological response to oxidative stress, research has shown that Nrf2 has anti-inflammatory property by increasing the transcription of antioxidant genes (Sethi et al. 2025). Nrf2 is abundant in the cytoplasm but is transported to the nucleus

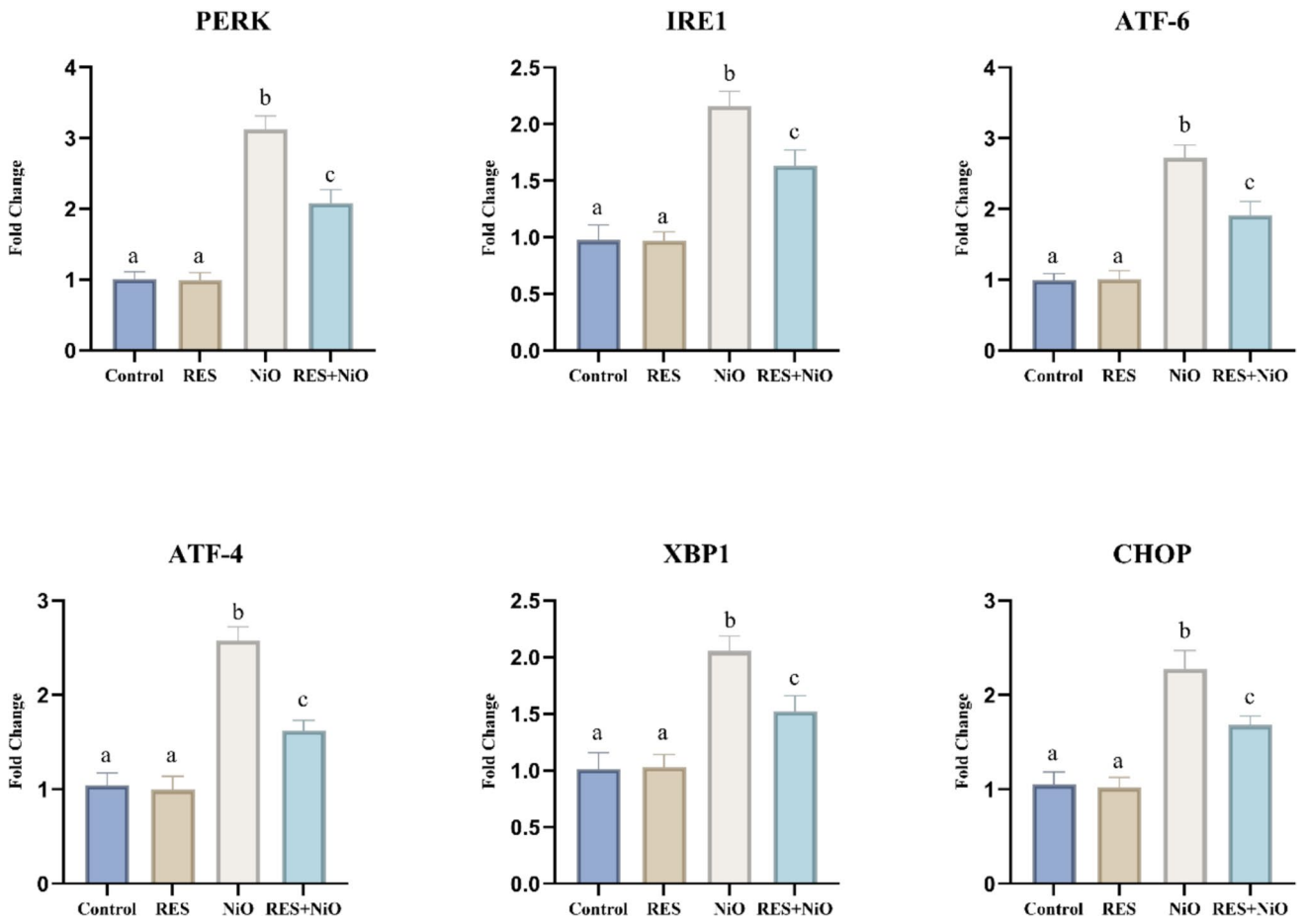


Fig. 7 Relative mRNA transcript levels of PERK, ATF-6, ATF-4, IRE1, XBP1, and CHOP and statistical analysis among experimental groups. Results are given as mean ± SD ($n = 6$). Results are accepted as statistically significant when the $p < 0.05$. Different letters given as superscripts in each row indicate significance between groups

during oxidative stress caused by increased ROS (Shaw and Chattopadhyay 2020). Upon nuclear translocation, Nrf2 binds to the Antioxidant Response Element (ARE). This binding activates a cellular defense pathway dependent on Nrf2, which upregulates enzymes like heme oxygenase-1 (HO-1) and glutamyl (Sethi et al. 2025). Previous research has demonstrated Heme oxygenase (HO-1) to have anti-inflammatory, antioxidant, and antiapoptotic properties and is critically important in oxidative stress, inflammation, and disease progression (O'Rourke et al. 2024). Studies have also reported that HO-1 improves mitochondrial function by reducing ROS (Even et al. 2018). Antioxidants such as SOD, CAT, GPx, and GST are known as primary antioxidants in cellular defense, and potential changes in their activities during oxidative stress promote oxidative damage (Karaboduk and Kalender 2021; Fidan et al. 2024). SOD is the first step in the cell against free radicals, catalyzing the superoxide radical to molecular oxygen and H_2O_2. CAT, on the other hand, decomposes the superoxide radicals converted to H_2O_2 by SOD into water and oxygen (Uzunhisarcikli et al. 2021; Dogan et al. 2025). GPx plays a role in the reduction of H_2O_2 to water, while GST is effective in the detoxification of xenobiotics and the reduction of H_2O_2 (Karaboduk et al. 2015; Apaydin et al. 2025). Previous studies have indicated that Ni induces oxidative stress and increases ROS in vivo studies, resulting in significant changes in antioxidant capacities (Alhazmi et al. 2024; El Brouzi et al. 2025). In the current study, NiO application caused a sharp reduction in Nrf2, HO-1, SOD, CAT, GPx, and GST enzyme activities, while resveratrol supplementation reduced NiO-induced toxicity and improved the parameters studied. The electron-donating properties of RES, thanks to its radical-scavenging power, may have reduced ROS levels by enhancing Nrf2/HO-1 activity (Elewa et al. 2025; Liu et al. 2025). Furthermore, the dissociation of Nrf2/Keap1 binding, coupled with increased Nrf2 expression and its localization to the nucleus, may have enhanced antioxidant defenses by increasing enzyme activities (Elewa et al. 2025).

Inflammation is a protective reaction to a variety of xenobiotic stimuli (Adiguzel et al. 2024). A linear correlation

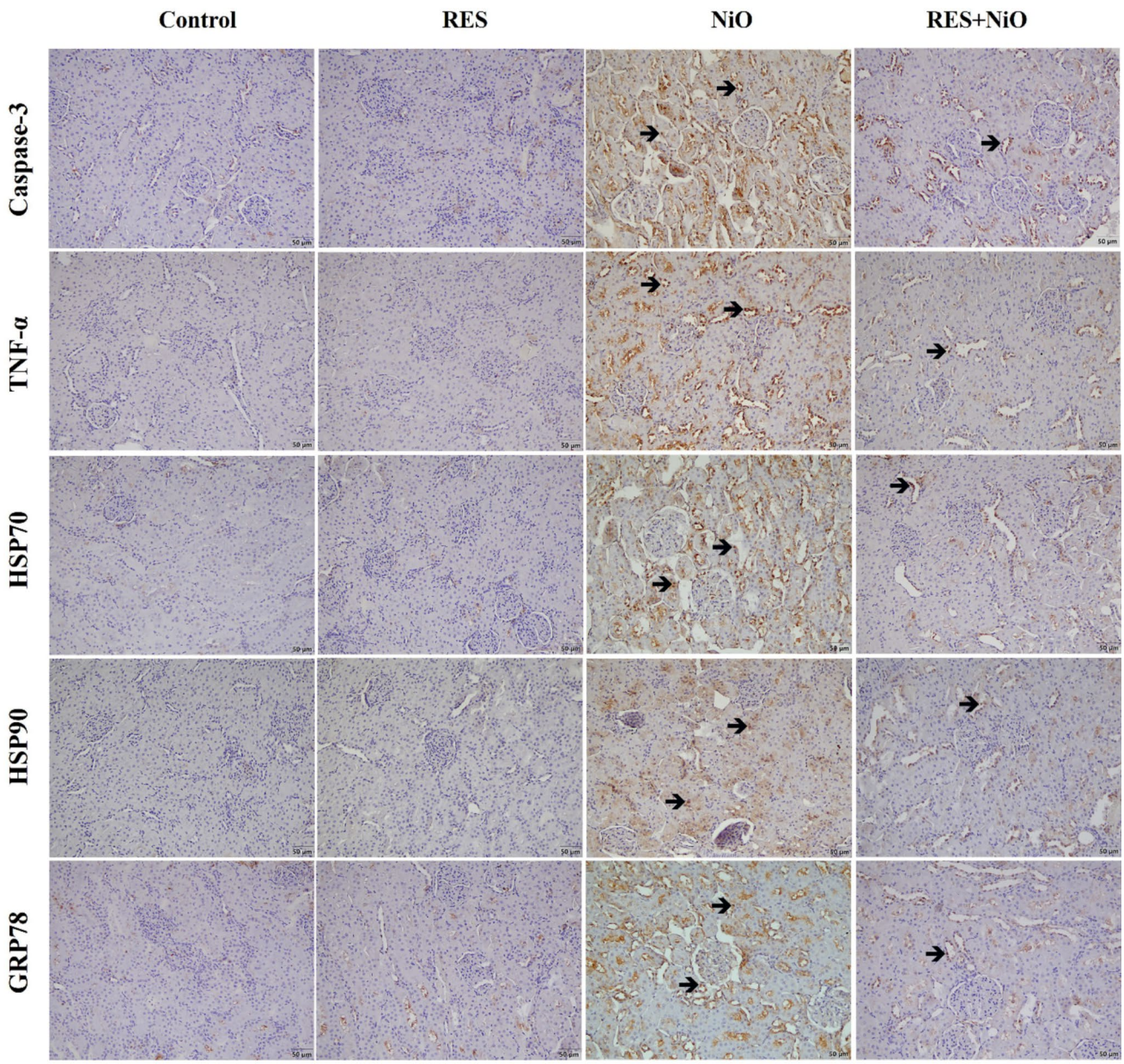


Fig. 8 Immunohistochemical staining of caspase-3, TNF-α, HSP70, HSP90, and GRP78 in kidney tissues. Control and RES groups showed weak staining for Caspase-3, TNF-α, HSP70, HSP90, and GRP78, while NiO and RES + NiO groups showed increased expression compared to control and RES groups, immunopositive cell (). Scale bar: 50 µm

exists between oxidative stress and inflammation, primarily driven by enhanced levels of reactive oxygen species (ROS) (Ayhan et al. 2025). Excessive ROS production can trigger the activation of NF-κB, a key transcription factor that regulates the expression of numerous pro-inflammatory genes (Rana et al. 2020). As a marker of inflammatory damage, NF-κB plays a central role in cytokine activation and immune responses. Upon activation, NF-κB translocates to the nucleus and induces the expression of pro-inflammatory cytokines, such as TNF-α and IL-1β, which are critical in initiating and sustaining inflammation (Şimşek et al. 2023). While IL-1β is one of the proinflammatory cytokines and mediates the release of numerous cytokines, TNF-α functions to activate immune cells by stimulating them during inflammation (Xu et al. 2021; El Brouzi et al. 2025; Ayhan et al. 2025). Previous studies suggest that Ni applications increase inflammation (Karaboduk et al. 2024a; Hassanen et al. 2025). In the current study, NiO elevated inflammation in rat kidney tissue. RES application reduced the inflammation caused by NiO. It has been reported that RES regulates

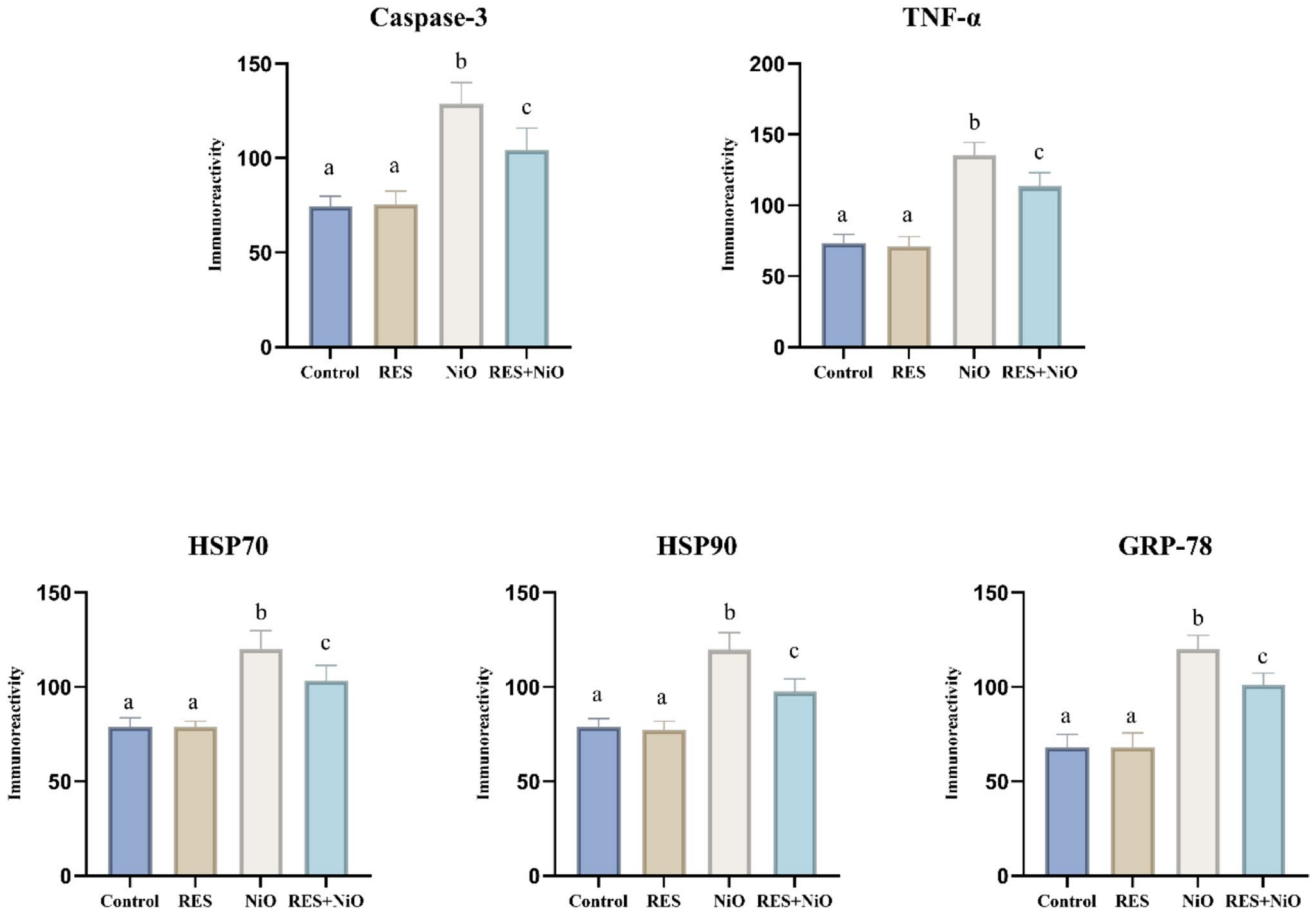


Fig. 9 Analysis of immunoreactive density in the kidney for caspase-3, TNF-α, HSP70, HSP90, GRP78. Results are accepted as statistically significant when the $p < 0.05$. Different letters given as superscripts in each row indicate significance between groups

nuclear factor κB (NFκB) through properties such as ROS scavenging and hydrogen peroxide suppression, thereby lowering the expression of proinflammatory cytokines IL-1β and TNF-α (Abdelrahman et al. 2022).

8-OHdG is an often-used marker for detecting ROS-induced DNA damage during oxidative stress (Graille et al. 2020). The DNA base guanine is extremely vulnerable to ROS, and during oxidative stress, 8-OHdG oxidizes guanine, causing DNA damage (Kandemir et al. 2025). There have been studies in the past showing that NiO raises 8-OHdG levels (Adiguzel and Karaboduk 2024; Alhazmi et al. 2024). In the current study, oxidative stress caused by NiO increased the level of 8-OHdG in kidney tissues. RES support significantly reduced this level.

Apoptosis is an important mechanism for eliminating damaged, aged, and dysfunctional cells (Venkatesan et al. 2025). Caspase-3 is also a key factor in oxidative stress-mediated apoptosis due to increased ROS (Hassanen et al. 2025). Prior studies have suggested increased apoptosis in nickel-induced in vivo experimental models (Yildiz Deniz et al. 2024; Mehanna et al. 2025). In the current study, NiO treatment elevated caspase-3 expression in rat kidney tissue due to stress caused by excessive ROS production. It has been stated that RES increases antioxidant defense and prevents apoptosis against environmental toxins and increased ROS (Yuluğ et al. 2013). In this research, the RES application significantly reduced caspase-3 expression, indicating that RES plays an active role in caspase-3 modulation.

The endoplasmic reticulum (ER) is an essential organelle that plays critical roles in protein synthesis, folding, and maturation, as well as in the maintenance of cellular homeostasis and xenobiotic detoxification (Varışlı et al. 2023). During infections, calcium imbalance, or other physiological and pathological conditions, the accumulation of unfolded or misfolded proteins within the ER lumen increases, leading to ER stress. To restore ER function, cells activate the unfolded protein response (UPR), a highly conserved adaptive signaling pathway (Cakmak et al. 2023). Heat shock proteins (HSPs) constitute a family of molecular chaperones classified according to their functions, including HSP60, HSP70, HSP90, and HSP110. Under normal physiological conditions, their expression levels are low; however, exposure to

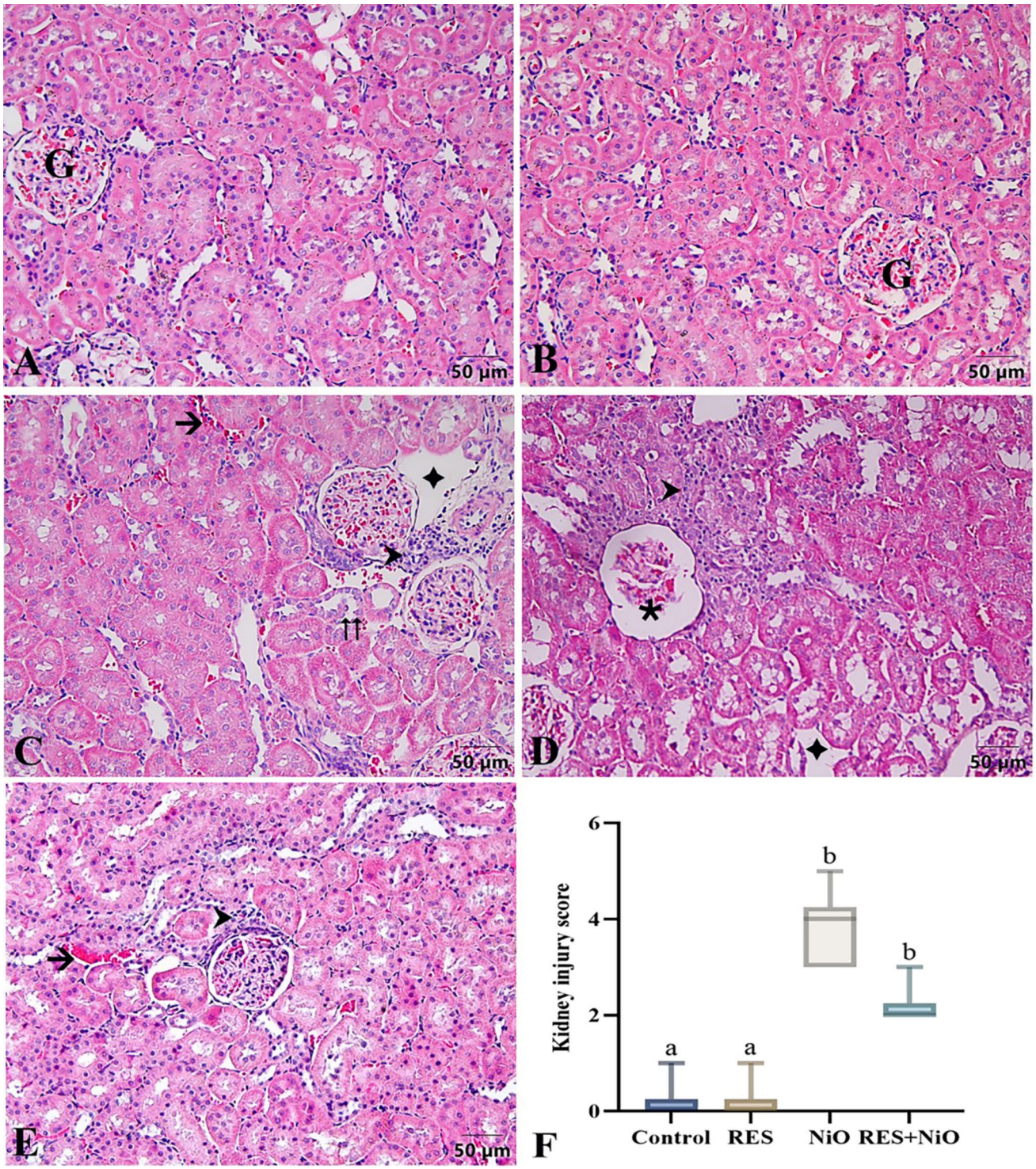


Fig. 10 H&E image of kidney tissue. **A** Control and **B** RES groups. The glomerulus (**G**) and tubules appear to have a normal histological structure. **(C–D)** NiO group showed tubular degeneration ( ), inflammatory cell infiltration ( ), hemorrhage ( ), glomerular degeneration ( ) and edema ( ) in kidney. **E** RES + NiO group showed inflammatory cell infiltration ( ), hemorrhage ( ) in kidney. **F** Statistical analysis of kidney injury scores. Scale bar = 50 µm, $p < 0.05$

cellular stress markedly induces their expression (Kandil et al. 2024). Among these, HSP70 plays a central role in ensuring proper protein folding, whereas HSP90 is involved in maintaining proteins in their functional conformations (Akin et al. 2025). In addition, glucose-regulated protein 78 (GRP78) is a key ER-resident chaperone that regulates

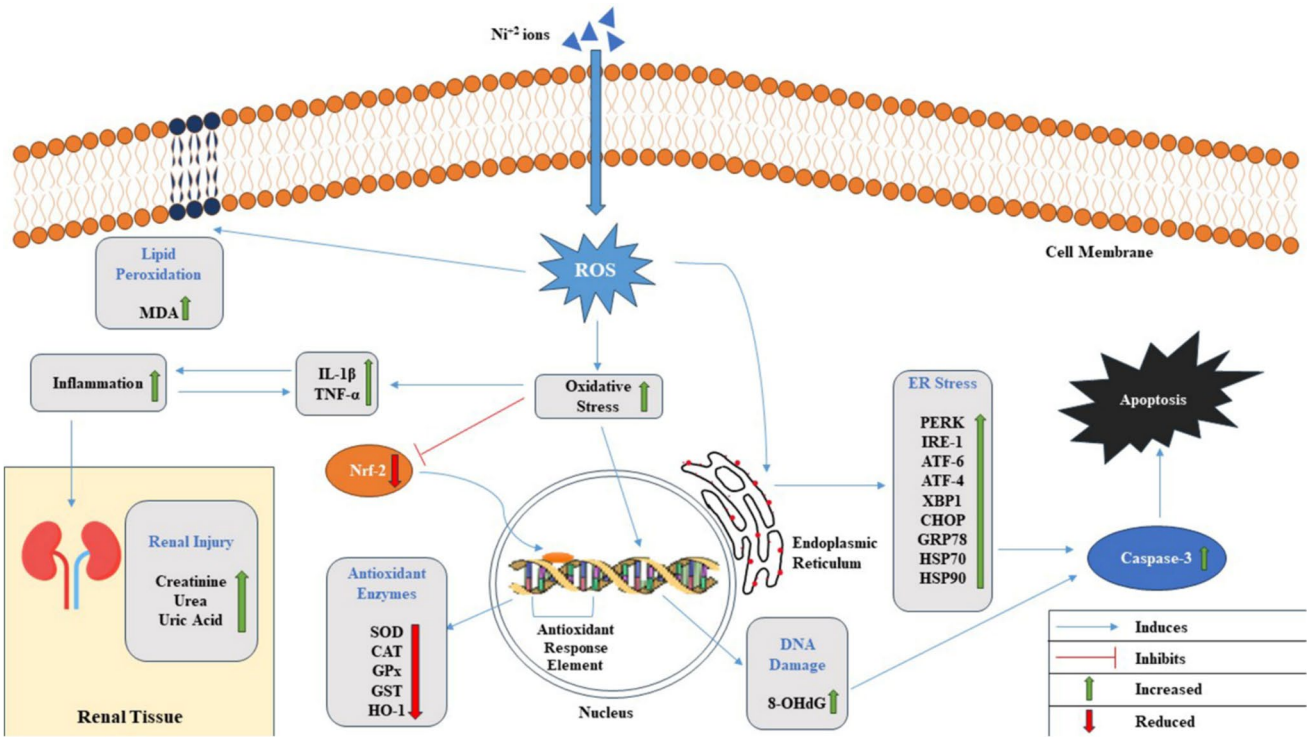


Fig. 11 Schematic diagram illustrating the toxic mechanism of nickel

protein folding and serves as a critical signaling regulator during ER stress (Yang et al. 2025b). Under endoplasmic reticulum (ER) stress, the unfolded protein response (UPR) is activated through three distinct transmembrane sensor proteins: protein kinase RNA-like ER kinase (PERK), inositol-requiring enzyme 1 (IRE1), and activating transcription factor 6 (ATF6) (Cakmak et al. 2023). Under normal physiological conditions, these sensors are bound to the ER chaperone glucose-regulated protein 78 (GRP78); however, ER stress leads to the dissociation of GRP78 and subsequent activation of these signaling pathways. Activation of PERK promotes the induction of activating transcription factor 4 (ATF4), whereas IRE1 activation results in the splicing and activation of X-box binding protein 1 (XBP1), thereby coordinating adaptive responses to restore ER homeostasis (Tatar and Tatar 2019; Varışlı et al. 2023). C/EBP homologous protein (CHOP) is expressed at very low levels under physiological conditions and contributes to the maintenance of cellular homeostasis; however, under prolonged or pathological ER stress, CHOP expression is markedly upregulated and functions as a key mediator of ER stress–induced apoptosis, facilitating the removal of irreversibly damaged cells (Hu et al. 2019). Accumulating evidence indicates that nickel exposure induces ER stress in both rats and mice, leading to the activation of UPR-associated signaling pathways and apoptotic responses (Chang et al. 2017; Zhou et al. 2023). In this study, NiO exposure significantly increased the expression of the chaperone proteins HSP70, HSP90, and GRP78, as well as the genes PERK, ATF6, IRE1, ATF4, XBP1, and CHOP in rat kidney tissue, indicating the induction of ER stress. Resveratrol (RES) supplementation markedly modulated the expression of these genes, demonstrating a protective effect against NiO-induced ER stress. This effect is thought to be related not only to the antioxidant properties of RES but also to its ability to suppress excessive UPR activation.

Exposure to heavy metals and other xenobiotics leads to severe histopathological changes in living tissues (Kalender et al. 2004; Apaydin et al. 2015; Karaboduk et al. 2025). Many previous studies have shown that in vivo applications of nickel metal, depending on dose and time, cause oxidative stress by promoting lipid peroxidation and inhibiting antioxidant capacity, resulting in serious changes in the histoarchitectural structures of organs (Pan et al. 2024; Alhazmi et al. 2024; Hassanen et al. 2025). In the study conducted by Sharma et al. (2024), it was reported that repeated nickel dosing caused a decrease in body weight gain and serious organ damage with oxidative stress in the kidney tissue. In addition, metal toxicity causes tubular degeneration in the kidney tissue, causing serious deterioration in the tubule transport system and reabsorption functions, thus altering kidney functions (Şimşek et al. 2023). In the current study, NiO administration was observed to produce serious histopathological effects in rat kidney tissue. These changes

were paralleled by increases in urea, creatinine, and uric acid levels, key indicators of renal function and structural integrity, and by increased inflammation levels. RES treatment has been observed to improve NiO-induced renal histology. This is particularly reflected in the restoration of tubular and glomerular structures, improved biochemical values, and decreased inflammation.

Conclusion

In this study, subchronic NiO exposure lowered oxidative stress in experimental animals by elevating lipid peroxidation and decreasing antioxidant activity. It also led to increased inflammation, apoptosis, and endoplasmic reticulum stress markers. Administering RES (a flavonoid with antioxidant and anti-inflammatory properties) to the animals resulted in improvements in altered renal biochemistry, inflammation, apoptosis, and a significantly altered histological appearance. These results suggest that natural compounds such as RES could be used as potential therapeutic agents against renal toxicity resulting from NiO administration.

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Author contribution Conceptualization: Orkun Barsbek Olcekci, Caglar Adiguzel; data curation: Orkun Barsbek Olcekci; formal analysis: Orkun Barsbek Olcekci, Caglar Adiguzel; methodology: Caglar Adiguzel, Orkun Barsbek Olcekci; investigation and validation: Orkun Barsbek Olcekci; supervision: Caglar Adiguzel; writing—review and editing: Orkun Barsbek Olcekci, Caglar Adiguzel. All authors approved the final version of the manuscript. The authors declare that all data were generated in-house and that no paper mill was used.

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Data availability All data in the current study can be obtained from the corresponding author upon reasonable request.

Declarations

Ethics approval For this study, ethical approval (G.Ü.ET-24.044) was obtained from Gazi University Animal Experiments Local Ethics Committee.

Competing interests The authors declare no competing interests.

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