Bull. of Egyp. Soc. Physiol. Sci.

(Official Journal of Egyptian Society for Physiological Sciences)

(pISSN: 1110-0842; eISSN: 2356-9514)

Irisin /resveratrol combination ameliorates cisplatin induced acute kidney injury in rats: spotlight on ferroptosis and Nrf2/MIOX pathways

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Submit Date : 24 July 2025
Revised Date :6 August 2025
Accept Date : 14 August 2025

Keywords

- Irisin
- Resveratrol
- Cisplatin-induced AKI
- Ferroptosis
- Nrf2

Abstract

Background & aim: Cisplatin-induced acute kidney injury (AKI) is a serious condition with high morbidity and mortality. This study aimed to investigate the therapeutic role of irisin and resveratrol either individually or in combination in cisplatin-induced AKI focusing on ferroptosis and the potential involvement of nuclear factor erythroid 2–related factor 2 (Nrf2) and Myo-inositol oxygenase (MIOX). Methods: Thirty male Wistar rats were divided into five groups: control, cisplatin, irisin + cisplatin, resveratrol + cisplatin, and combined irisin/resveratrol + cisplatin. AKI was induced by a single intraperitoneal injection of cisplatin (8 mg/kg). Irisin (1 mg/kg) and resveratrol (10 mg/kg) were administered intraperitoneally 30 minutes after cisplatin and again on day three. On day five, blood and kidney tissues were collected for biochemical, histopathological and immunohistochemical assessments of B cell lymphoma 2 apoptosis regulator (Bcl-2). Renal function markers (renal index, serum creatinine and blood urea nitrogen [BUN}), oxidative stress parameters (reduced glutathione [GSH}, malondialdehyde [MDA], glutathione peroxidase [GPX]), inflammatory cytokines (tumor necrosis factor-α [TNF-α], interleukin 6 [IL-6]), and ferrous iron levels were measured. Gene expression of Nrf2 and MIOX was analyzed by quantitative reverse-transcription polymerase chain reaction (qRT-PCR). Results: Treatment with either irisin or resveratrol significantly improved renal function, reduced oxidative stress, inflammation, ferroptosis markers and MIOX expression, while enhancing GPX4 activity, Nrf2, and Bcl-2 expression. While their combination was more pronounced versus each agent alone. Conclusion: The enhanced effect of irisin /resveratrol combination may be attributed to their complementary antioxidant, anti-inflammatory, and anti-apoptotic actions, along with their ability to regulate ferroptosis

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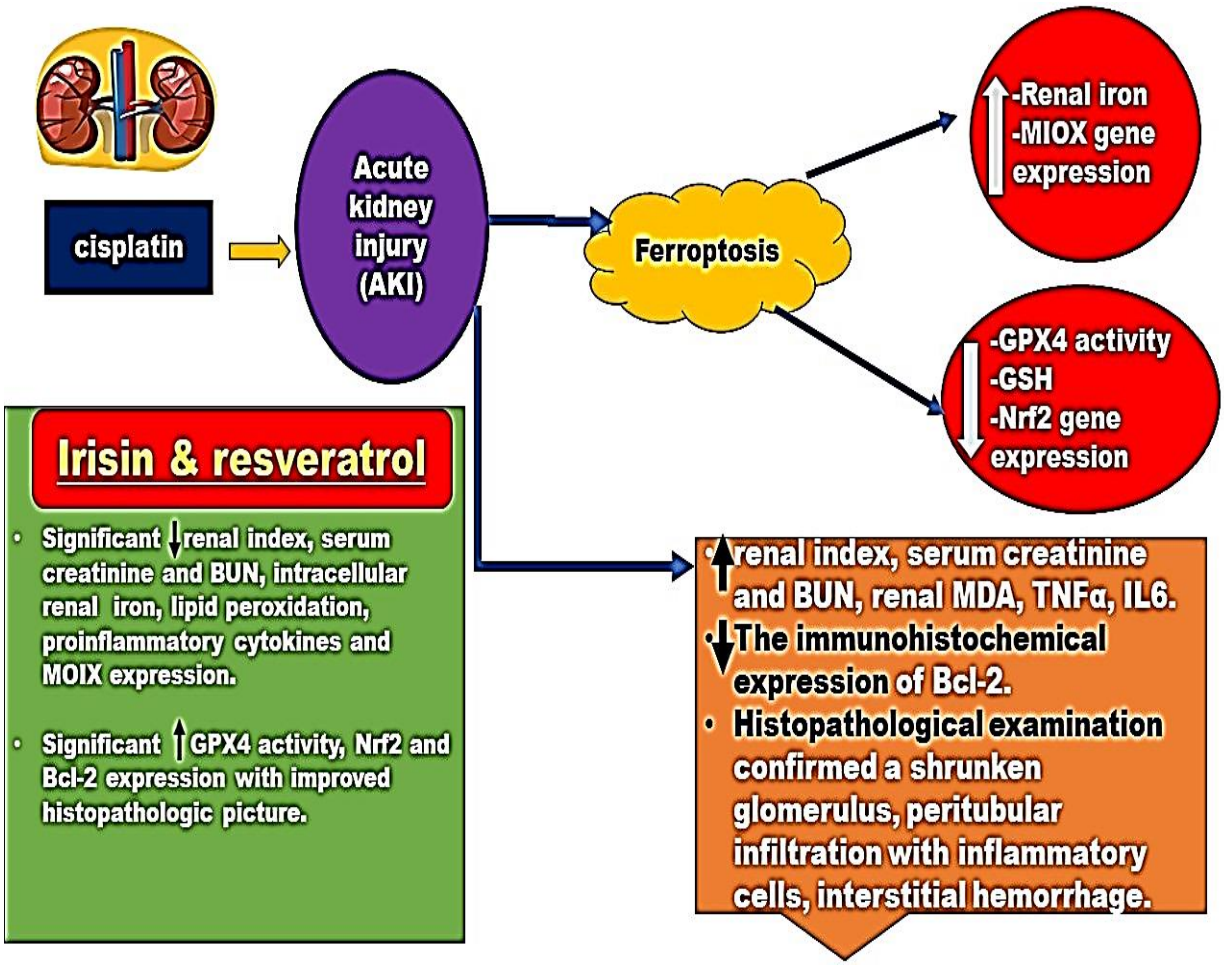


Introduction

Acute kidney injury (AKI) is a widespread medical condition characterized by a sharp decrease in function of kidney, leading to the retention of toxins and metabolic waste in the body. This impairment can cause serious health complications and affect the function of other organs. AKI poses a major global health challenge due to its high fatality rate, significant treatment expenses, and elevated risk of progression to chronic kidney disease (CKD), making it an urgent area of medical research[1].AKI can be initiated and progressed by several pathogenic circumstances, as ischemia-reperfusion injury, nephrotoxic drugs like cisplatin, rhabdomyolysisandinfection. However, the specific process of it is still unknown[2].

There are currently no proven therapeutic approaches to stop AKI from developing, decrease its course, or aid in its recovery. For therapeutic treatment, it is therefore essential to thoroughly examine the unique pathophysiology of AKI and create new corresponding medications[3].AKI caused by cisplatin (Cis) is distinguished with a complex set of events that include oxidative injury, inflammation, and an imbalance between autophagy and apoptosis[4].

Ferroptosis, a new process of non-apoptotic cell death, is contingent upon iron and results from the accumulation of lipid peroxides within cells. AKI has been demonstrated in numerous studies to be significantly influenced by ferroptosis, as opposed to other forms of cell death such as apoptosis, necroptosis, and pyroptosis. Therefore,

it is essential to look into the mechanism of ferroptosis in renal tubular cells in AKI [5].

The enzymatic activity of myo-inositol oxygenase gene (MIOX) that is an enzyme found in the renal proximal tubular cytosol is elevated by its phosphorylation. The promoter of this gene has oxidant, carbohydrate, osmotic, sterol, and components of the antioxidant response; as a result, elevated glucose, osmolytes that are organic, oxidative stress and fatty acids, all impact its transcription[6].

Exercise secretes irisin, a muscle factor that is crucial for controlling fat browning, enhancing metabolism of liver andmetabolism of glucose in the body, preserving homeostasis of the muscles and bones, encouraging expansion of synapses, and slowing the spread of cancer. It is unclear, therefore, how ferroptosis and irisin, one of myokines implicated in autophagic process and metabolism of ROS, are related[7].

Several studies showed that irisin exerted an antioxidant effect, reducing inflammation and apoptosis in various conditions[8]. But according to our knowledge, there is no study that clarifies the role of irisin in cases of AKI by cisplatin and its link to the process ferroptosis[9].

A flavonoid called resveratrol has been extracted from a variety of foods, comprising peanuts, red wine, berries, and grapes[10]. Resveratrol's medicinal benefits have drawn attention to its potential as a nutraceutical ingredient in recent years [11]. Hepatoprotective, anti-diabetic, anti-cancer, antioxidant, anti-inflammatory, cardioprotective, and capable of reducing dyslipidemia are just a few of the many pharmacological effects of this natural polyphenol [12]. Its antioxidant activity may be primarily responsible for these remarkable therapeutic results. Numerous experimental studies have suggested that resveratrol may change cell signaling linked to inflammation and oxidative stress[13].

According to reports, resveratrol has beneficial effects in several chemotherapy induced organ toxicity through attenuating ferroptosis such as 5-FU-induced cardiotoxicity[14-15]and Dox induced cardiotoxicity [16]. These findings motivate us to look into whether resveratrol's beneficial effect against cisplatin-induced AKI was correlated with attenuating ferroptosis.

One essential antioxidant transcription factor that can control a number of cytoprotective factors possesses antioxidant property is nuclear factor erythroid related factor- 2 (Nrf2)[17]. With an emphasis on the function of Nrf2 in mediating the renal protective effect of irisin and resveratrol, the aim of the current study is to elucidate the role of these compounds in cases of AKI caused by cisplatin and its connection to the ferroptosis process.

1. Chemicals and Methods

2.1. Animals and ethics

Thirty adults male Wistar rats of weight (200±50 g) were provided by Tanta University's Faculty of Medicine's local animal care Centre. Throughout the experiment and the 10 acclimatization days that preceded it, the rats were retained at ambient temperature in clean, well-ventilated steel cages under strictly controlled (12/12-h) light/dark cycles. They also hadregular access torat feed and tap water. With a code of ethics for approval of36264PR1007/12/24, the Animal Research Ethical Committee at Tanta University's Faculty of Medicine verified this

study, which closely followed the National Institutes of Health's guidelines for the use and care of experimental animals (NHI Publication; No. 8023, revised 1996).

2.2. Chemicals and Drugs

Sigma Aldrich provided the Cisplatin (purity ≥98%, CAS#15663-27-1), Irisin (purity ≥95%, CAS#1465928-51-1), Resveratrol (≥99%, CAS# 501-36-0) as well as the other chemicals and solvents used(St. Louis, MO, USA).None of them needed additional purification because they were all of high analytical grades.

2.3. Experimental Design

Five experimental groups of 6 rats each were divided up into the following categories:

1. GroupI (control group): on days one and three, the rats in this group received an intraperitoneal injection of 0.9% saline (10 ml/kg).
2. Group II (Cisplatin- group): On day one, (8 mg/kg) cisplatin were injected intraperitoneal, and on day 3, (10 ml/kg)of 0.9% saline were injected[18].
3. Group III (treated with Irisin): On day one, each rats in this group received 1 mg/kg irisin intraperitoneal 30 minutes after receiving (8 mg/kg) Cisplatin, and on day threethey received an injection of 1 mg/kg irisin[19].
4. Group IV (treated withResveratrol): On day one: 30 minutes after receiving (8 mg/kg) cisplatin,each rat was injected with 10 mg/kg resveratrol intraperitoneal, and on day three they received 10 mg/kg resveratrol[20].
5. Group V (treated with bothResveratrol and Irisin): On day one, cisplatin (8 mg/kg) was administrated to the rats in this group, 30 min later an intraperitoneal injection of irisin and resveratrol (1mg/kg), (10 mg/kg) respectively, but on day three only an injection of irisin (1mg/kg) and resveratrol (10 mg/kg) were done.

Prior to anesthesia on the fifth day of the therapy, the rats were weighed in order to determine their renal index (RI)[21].

2.4. Blood and Tissue Sampling

At the conclusion of the experimental phase, rats were anesthetized with sodium barbiturate (60 mg/kg, IP) [22]. While heartbeats could still be heard, a cardiac puncture was used to get the blood sample. Following clotting at room temperature, blood samples underwent centrifugation at 5000 rpm for 10 minutes to obtain sera, which were then aliquoted and stored at -80°C until further analysis. For tissue collection, the thorax and abdomen were longitudinally opened, allowing careful extraction of the kidneys. After weighing, the kidneys were meticulously rinsed with ice-cold phosphate-buffered saline (PBS). The right kidneys were diced into small fragments and processed differently depending on the intended assay: homogenization in PBS (50 mM, pH 7.4) for ELISA preparations, or in RNA lysis buffer for qRT-PCR studies. Meanwhile, the left kidneys from all rats were fixed in 10% formalin prepared in PBS for subsequent histopathological examination. All processed samples were preserved at -80°C until needed for experimentation.

2.5. Biochemical assays

2.5.1. Assessment of renal function.

Utilizing colorimetric kits obtained from Biodiagnostic Co., Cairo, Egypt, serum creatinine and blood urea nitrogen (BUN) levels were assessed in addition to the kidney index which was calculated following the equation

Renal Index=kidney weight/body weight.

2.5.2 Evaluation of iron overload

A commercial ferrous iron assay kit (Cat# E-BC-K304-S) from Elabscience Biotechnology Co., Houston, TX, USA, was used to measure renal Fe^{+2} calorimetrically. This kit releases Fe^{+2} when acidic buffer is added, and it reacts with a chromogen (bipyridine) to produce a colorimetric product that is proportionate to the iron concentrations in the sample.

2.5.3. Assessment of renal redox status, inflammation.

A commercial kit (Biodiagnostic Co, Egypt) was used to colorimetrically measure the kidneys' GSH levels at 405 nm. In short, 5,5′-Dithiobis (2-nitrobenzoic acid) (DTNB) is reduced by GSH to a yellow reduced chromogen that is directly proportional to the GSH concentration. The renal glutathione peroxidase (GPX) enzyme's activity was indirectly measured using the UV spectrophotometric technique because the oxidation of NADPH to NADP+ is accompanied by a decrease in absorbance at 340 nm (A340). The molar extinction coefficient for NADPH at 340 nm, using kits bought from Biodiagnostic, Egypt, is 6220 M-1 cm-1.

The amount of renal malondialdehyde (MDA) was colorimetrically measured using a thiobarbituric acid (TBA)-dependent method that measured thiobarbituric acid reactive compounds at 532 nm. The results were expressed as nmol/gm tissue and were calculated using the MDA-TBA complex's extinction coefficient, $1.56 \times 105\ M{-}1\ cm{-}1$.

Rat-specific ELISA kits (Cat# MBS2508238, MBS269892) purchased from MyBioSource Company, San Diego, USA, were utilized to measure the amounts of interleukin 6 (IL-6) and tumor necrosis factor-α (TNF-α) in renal tissue homogenate. Procedures were developed using the Stat Fax®2100 ELISA Reader (Fisher Scientific, Dardilly, France) and followed the given guide.

2.5.4. Quantitative reverse transcription PCR (qRT-PCR)

Total RNA isolation was executed utilizing the Gene JET RNA Purification Kit (Thermo Scientific, #K0731, Waltham, MA, USA) on frozen renal tissues from each experimental group. A Nano Drop spectrophotometer (Wilmington, NC, USA) was utilized for measuring absorbance at 260 nm and compute the OD260/280 ratio to estimate the amount and purity of the extracted RNA. The resulting cDNA was then utilized as a template for SYBR Green-based qPCR after cDNA synthesis was completed using Revert Aid H Minus Reverse Transcriptase (Thermo Scientific, #EP0451). A Step One Plus real-time PCR system (Applied Biosystems, USA) was used for the amplification. It started with 10 minutes of denaturation at 95°C, and then went through 40–45 cycles that included denaturation at 95°C for 15 seconds, annealing at 60°C for 30 seconds, and extension at 72°C for 30 seconds. At 95°C, a melting curve analysis was performed to confirm the product's specificity. MIOX and Nrf2 mRNA expression levels were measured in relation to the housekeeping gene, β-Actin. As indicated in **Table 1**, primer sequences were produced using Primer3Plus software, and the 2^−ΔΔCt method was utilized for analyzing gene expression data.

Table 1: Sequence specific primers designed for qRT-PCR:

Gene	Primer sequence
Nrf-2	F:5'-GGCTACGTTTCAGTCACTTG-3' R: 5'-AACTCAGGAAT GGATAA-TAG-3'
MIOX	F: 5´- TCCGAAACTACACTTCAGGC-3´ R: 5´- CAGATGGAACCAGTCCTTGT -3´
β-Actin	F: 5´-GGCTGTGTTGTCCCTGTAT-3´ R: 5´-CCGCTCATTGCCGATAGTG-3´

2.6. Histopathological examination of the kidney

The renal tissue histological grading system was utilized for evaluating the histological outcomes of each group. With a binocular Olympus CX31 microscope, random high microscopic fields were inspected in order to assess the histopathological lesions. Normal histological structure is represented by zero, a tiny focal wounded area by 0.5, less than 10% of the cortex injured zone by 1, and 10% to 25% of the cortical injured region by 2. Between 25 and 75 percent of cortical damaged regions are represented by three, and above 75 percent of wounded regions are represented by four. For this assessment, the pathological signs of tubular epithelial degeneration, glomerular congestion and atrophy, and infiltrating interstitial inflammatory cells were done[23].

2.7. Immunohistochemical analysis for Bcl-2.

For assessment of the immunoreactivity of Bcl-2 in rat kidney tissues, the tissues were fixed in a 10% formaldehyde solution and then blocked in paraffin by passing through graded alcohols, methyl benzoate, and benzoles. A diluted 1/100 anti-Bcl-2 (B-cell lymphoma 2, ab194583) primary antibody was applied for one hour at room temperature in a humid environment to test for Bcl-2 immunoreactivity on 5μm slices from paraffin blocks [24].

The tissues in the negative control group were only treated with phosphate buffer solution. After the primary antibodies were incubated, one of the indirect methods—the Streptavidin-biotin peroxidase technique—was utilized. The sections were incubated at room temperature for 15 minutes after HRP streptavidin (Invitrogen Histostain plus Broad Spectrum –AEC, Ref. 85.9943) was applied. AEC (3-amino-9-ethylcarbazole) solution was applied to the sections that were going to be used for the chromogen application. After immunoreactivity control and light microscopy analysis of the sections, the reaction was deactivated utilizing distilled water according to the immunoreactivity status. Following their immersion in hematoxylin for negative staining, the sections were subsequently covered with a lamella using a water-based adhesive (Lab Vision, Large Volume Vision Mount, TA-060-UG) [25].Image analysis software (Image J,1.46a, NIH, Bethesda, MD, USA) was used to quantify immunohistochemical photographs [26]. Each slide had ten nonoverlapping fields (400) that were analyzed for the mean area percentage (%) of Bcl-2 immunostaining reaction.

The sacrificed animals will be packed in a special package according to safety precautions and infection control measures and will be sent with hospital biohazard[27].

Statistical analysis

The previously mentioned data were statistically expressed as the mean ± standard deviation. Statistical comparison between different groups was carried out by using one–way ANOVA. Significant results of analysis of variance were subjected to post hoc analysis (Tukey-Kramer multiple comparisons).

P-values <0.05 were considered statistically significant.

All statistical calculations were done using computer program SPSS (Statistical Package for the Social Science; SPSS Inc., Chicago, IL, USA) for Microsoft Windows (version 25).

2. Results

3.1. Protective effects of irisin and resveratrol on cisplatin-induced renal injury.

Fig. 1 illustrates the results of AKI biomarkers, which proved the nephrotoxic action of cisplatin. In contrast to control groups I, the Cis-induced nephrotoxicity group showed a significant rise in renal index Figure (1A), serum creatinine Figure (1B), and serum BUN Figure (1C). All were significantly greater than the control group and lower than the Cis group in both the irisin and resveratrol groups. Furthermore, out of all the groups under study, with the exception of the control groups, the irisin + resveratrol group showed the statistically significant lowest values.

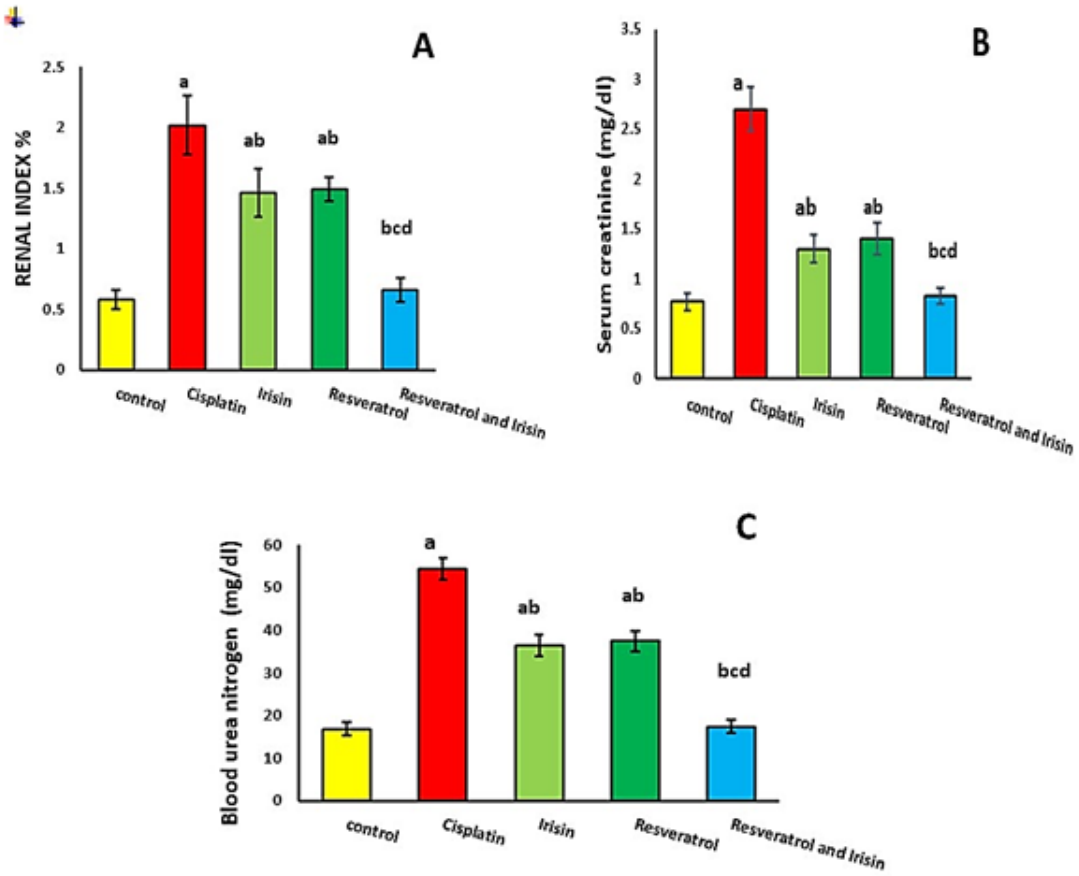


Fig. 1: AKI biomarkers Renal index., serum creatinine, and serum BUN in all studied groups.

The data are expressed as mean± SEM. A significant statistical difference is shown by the superscripts [a, b, c,] and [d] at P < 0.05. [a] p<0.05 versus. Control I, [b] p<0.05 versus Cis II, [c] p<0.05 versus Irisin III, and [d] p<0.05 versus Resveratrol IV using Tukey's post hoc test and one-way ANOVA.

3.2. Irisin and Resveratrolameliorated cisplatin-induced renal oxidative stress and inflammation.

Cis-induced cytotoxicity is mostly caused by cellular inflammation and redox imbalance, according to earlier study. This was evaluated in the current study by identifying the inflammatory biomarkers (TNF-α, IL6) and OS biomarkers (MDA, GPX, GSH) in renal tissue homogenate. Cis caused a statistically significant decline in renal GSH and GPX along with a significant rise in renal MDA, TNF-α, and IL6. However, the previously mentioned Cis-induced effects were considerably avoided when either Irisin or Resveratrol was administered. As seen in **Table 2**, the irisin + resveratrol group's results did not differ significantly from control I.

Table 2: Oxidative stress and inflammatory marker parameters in every group under study

Parameters/ Groups	Control group	Cisplatin group	Irisin group	Resveratrol group	Irisin+resveratrol group
Renal MDA (nmol/gm tissue)	17.55±1.56	36.88± 2.24 [a]	24.17± 2.12 [a, b]	22.17±1.96 [a, b]	18.61±1.72 [b, c, d]
Renal GPX (U/gm tissue)	12.7± 1.23	6.03± 0.52 [a]	9.86± 1.09 [a, b]	10.29±1.13 [a, b]	12.56±1.08 [b, c, d]
Renal GSH (mmol/gm protein)	13.6± 1.07	5.16± 0.62 [a]	10.78± 1.17 [a, b]	11.13± 1.12 [a, b]	13.06± 1.4 [b, c, d]
Renal TNF-α (pg/ mg protein)	5.7± 1.03	35.4± 1.83 [a]	13 ± 1.07 [a, b]	12.3± 1.1 [a, b]	7.48 ±0.8 [b, c, d]
Renal IL6 (Pg/ml protein)	36.36±2.92	111.2±10.01 [a]	49.42±3.69 [a, b]	51.5± 4.05 [a, b]	38.7± 3.21 [b, c, d]

The data are expressed as mean± SEM. A significant statistical difference at ($P < 0.05$) is revealed by the superscripts **[a, b, c,]** and **[d].** employing a one-way ANOVA and the Tukey post hoc test, **[a]**$p<0.05$ versus Control I, **[b]** $p<0.05$ versus Cis II, **[c]** $p<0.05$ versus Irisin III, and **[d]** $p<0.05$ versus Resveratrol IV. TNF-α: Tumor necrosing factor-alpha, GPX: glutathione peroxidase, GSH: reduced glutathione, IL6: interleukin-6, and MDA: malondialdehyde.

3.3. Irisin and Resveratrolameliorated cisplatin-induced renal iron.

The renal ferrous value was noticeably rise in the Cis group than in the control group. However, the previously mentioned Cis-induced effects were considerably avoided when either Irisin or Resveratrol was administered. As seen in **Fig. 2**, the irisin + resveratrol group's results were not different significantly from those of the control group.

3.4 beneficial effects of irisin and resveratrol on the expression of the MIOX and Nrf2 genes in response to cisplatin-induced kidney injury.

Fig.3: shows how MIOX and Nrf2 gene expression results demonstrated cisplatin's nephrotoxic effects. The Cis group's renal MIOX was significantly greater than that of the normal control group. Nevertheless, the Cis-induced adverse effects were significantly prevented when either Irisin or Resveratrol was taken. The results of the irisin + resveratrol group and the control I

group did not differ significantly, as seen in **Fig. 3A**. Renal Nrf2 was significantly reduced in the Cis group than in the normal control group. Nevertheless, taking either irisin or resveratrol significantly lowered the effects of Cis. The results of the irisin + resveratrol group did not differ significantly from those of the control I group, as illustrated in **Fig. 3B**.

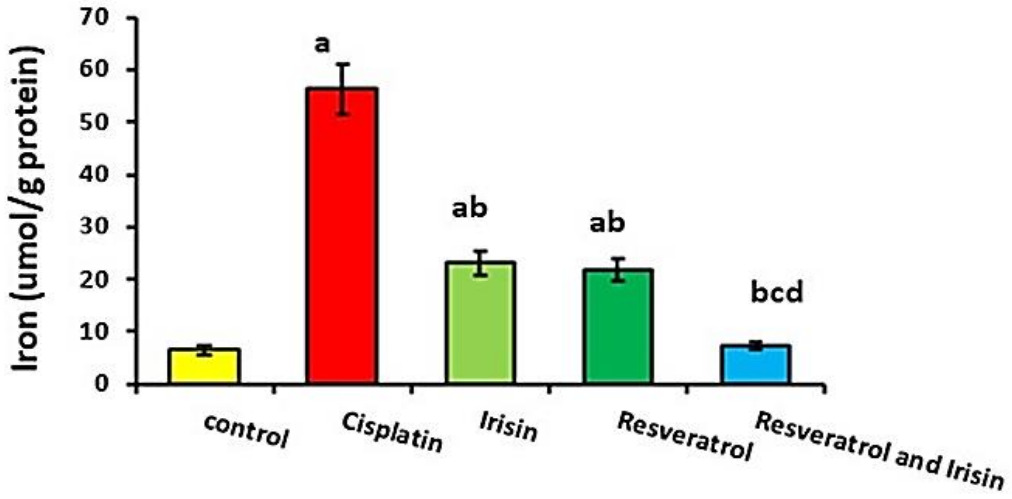


Fig. 2: Effect of Irisin & resveratrol on renal Iron (Umol/g protein) in all studied groups.
The data are expressed as mean± SEM. A significant statistical difference is shown by the superscripts [a, b, c,] and [d] at P < 0.05. [a] p<0.05 versus. Control I, [b] p<0.05 versus Cis II, [c] p<0.05 versus Irisin III, and [d] p<0.05 versus Resveratrol IV using Tukey's post hoc test and one-way ANOVA.

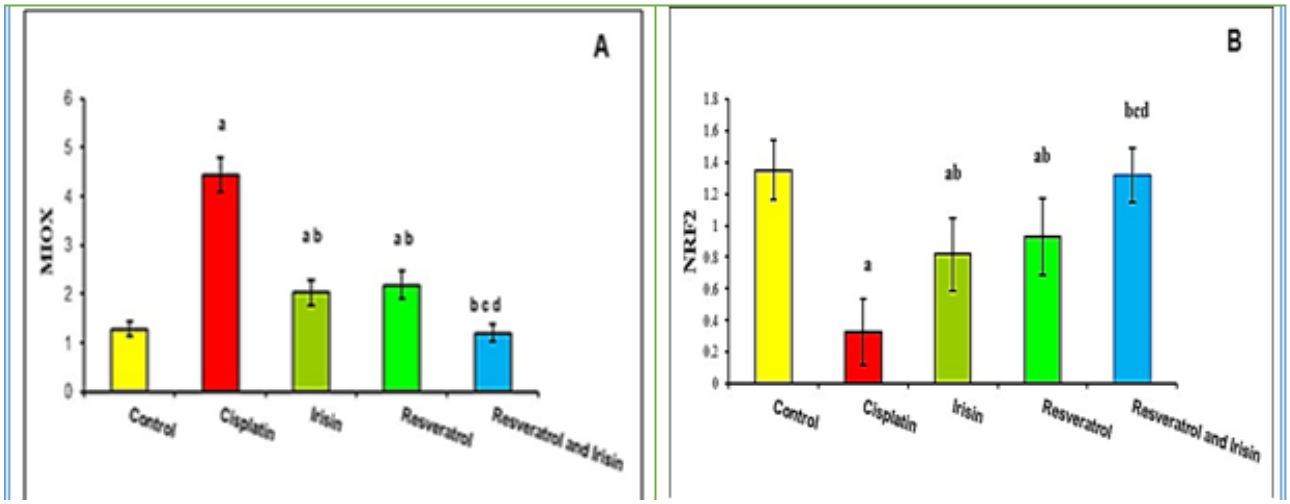


Fig. 3: Gene expression of MIOX and Nrf2 in all studied groups.
The data are expressed as mean± SEM. A significant statistical difference is shown by the superscripts [a, b, c,] and [d] at P < 0.05. [a] p<0.05 versus. Control I, [b] p<0.05 versus Cis II, [c] p<0.05 versus Irisin III, and [d] p<0.05 versus Resveratrol IV using Tukey's post hoc test and one-way ANOVA

3.5 Irisin and Resveratrol effect on renal tissue damage induced by Cisplatin H&E and Bcl-2 immunohistochemical assay: (Fig. 4&5&6)

The control group's histological analysis showed several glomeruli with a regular, continuous Bowman's capsule. Normal proximal convoluted tubules have brush borders and are

lined with big cuboidal cells and acidophilic cytoplasm. Wide lumens and cuboidal cell linings characterize distal convoluted tubules with score (0) (**Figures 4A to 4B& 5)**. However, the cisplatin group's histology analysis revealed a reduced glomerulus with a broad bowman's gap. Inflammatory cells have infiltrated the peritubules. Wide peritubular space and interstitial bleeding are observed. Both proximal and distal convoluted tubules exhibit vacuolated cytoplasm and lumen dilatation with score (4) which were highly significant compared to control group($p < 0.001$)**(Figures 4C to 4D& 5)**. According to histological examination, the cisplatin and irisin groups had mild renal structural deterioration, as evidenced by normal-looking glomeruli with normal Bowman's space. Bowman's space appears to be expanding, causing few glomeruli to appear reduced. With their brush border and acidophilic cytoplasm, the majority of proximal convoluted tubules seem normal. A small number of tubules have dilated lumen, although the distal convoluted tubules also seem normal with score (2) which showed significant decrease in the degeneration compared to Cisplatin group ($p < 0.05$) (**Figures 4E to 4F& 5**). Histological analysis of the cisplatin and resveratrol group revealed glomeruli that seemed to be normal, with large peritubular spaces and a normal Bowman's space. While some tubules exhibit lumen dilatation, proximal and distal convoluted tubules seem normal with score (2) which showed significant decrease in the degeneration compared to Cisplatin group ($p < 0.05$) (**Figures 4G to 4H& 5**). Histological analysis of the cisplatin, irisin, and resveratrol group revealed renal glomeruli that seemed to be normal, encircled by a large peritubular space and a normal Bowman's space. Large cuboidal cells line the proximal convoluted tubules, which have clear brush boundaries. With their large lumens and cuboidal cell lining, the distal convoluted tubules seem typical with score (0.8) which showed highly significant decrease in the degeneration compared to Cisplatin group ($p < 0.001$) (**Figures 4I to 4J& 5**).

The control group's immunohistochemical analysis revealed dense Bcl-2 immunostaining of the cortex and medulla's tubular lining epithelium. The cortex and medulla of the cisplatin group displayed mild Bcl-2 immunostaining of the tubular lining epithelium. The tubular lining epithelium in the brain and medulla exhibited moderate Bcl-2 immunostaining in the Cisplatin + irisin and Cisplatin + resveratrol groups. The tubular lining epithelium in the cortex and medulla had abundant Bcl-2 immunostaining in the cisplatin + irisin + resveratrol group, indicating that apoptosis was resolved(**fig. 6)**.

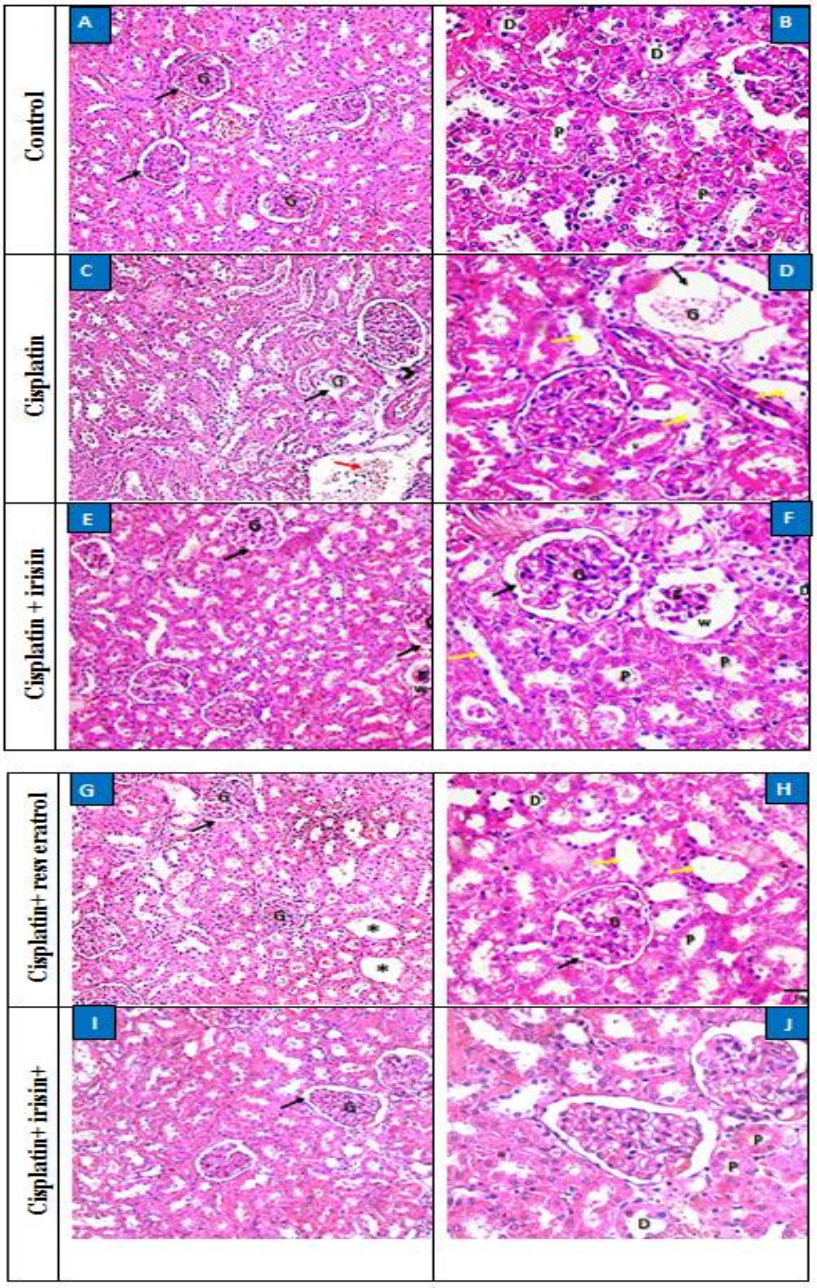


Fig.4: Histological examination of the kidney from studied groups. (A-B) Control group (group I) showed: (A) Multiple glomeruli (G) with a regular continuous bowman's capsule (black arrows), (B) Normal proximal convoluted tubules (P) lined with large cuboidal cells, acidophilic cytoplasm and having obvious brush borders and distal convoluted tubules (D) lined with cuboidal cells and having wide lumens. (C-D) Cisplatin group (group II) showed: (C) Shrunken glomerulus (G) with wide bowman's space (black arrow). There is peritubular infiltration with inflammatory cells (black arrow heads). Interstitial hemorrhage (red arrow) and wide peritubular space (asterisk) are noticed, (D) shrunken glomerulus (G) with dilated bowman's space (black arrow). Proximal and distal convoluted tubules show dilatation of their lumen (yellow arrows) and vacuolated cytoplasm (V). (E-F) Cisplatin and irisin group (group III) showed: (E) Moderate impairment of renal structure as glomeruli (G) appear normal with normal bowman's space (black arrows). Few glomeruli appear shrunken (g) with widening of bowman's space (w), (F) apparently normal glomeruli (G) with normal bowman's space (black arrow). Few glomeruli appear shrunken (g) with widening of bowman's space (w). Most proximal convoluted tubules appear normal (P) with acidophilic cytoplasm and brush border. The distal convoluted tubules (D) appear normal. Few tubules show dilated lumen (yellow arrows). (G-H) Cisplatin and resveratrol group (group IV) showed: (G) Apparently normal glomeruli (G) with normal bowman's space (black arrow). Wide peritubular spaces can be noticed (asterisks). (H) Normal glomeruli (G) with normal bowman's space (black arrow). Proximal convoluted tubules (P) and distal convoluted tubules (D) appear normal, but some tubules show dilatation in their lumen (yellow arrows). (I-J) Cisplatin, irisin and resveratrol group (group V) showed: (I) Apparently normal renal glomeruli (G) surrounded by normal bowman's space (black arrow). Wide peritubular space can be noticed (asterisk), (J) Proximal convoluted tubules (P) lined with large cuboidal cells and brush borders are obvious. The distal convoluted tubules (D) appear normal, lined with cuboidal cells and have wide lumens. Hematoxylin and eosin staining (A, C, E, G & I) (×200, scale bar = 100 μm) and (B, D, F, H & J) (×400, scale bar = 50 μm).

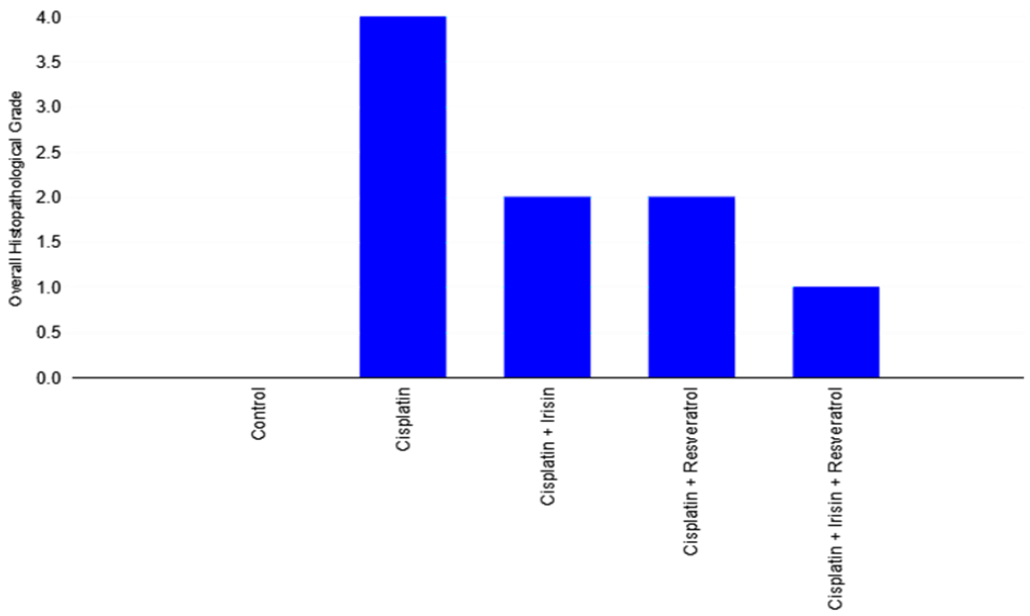
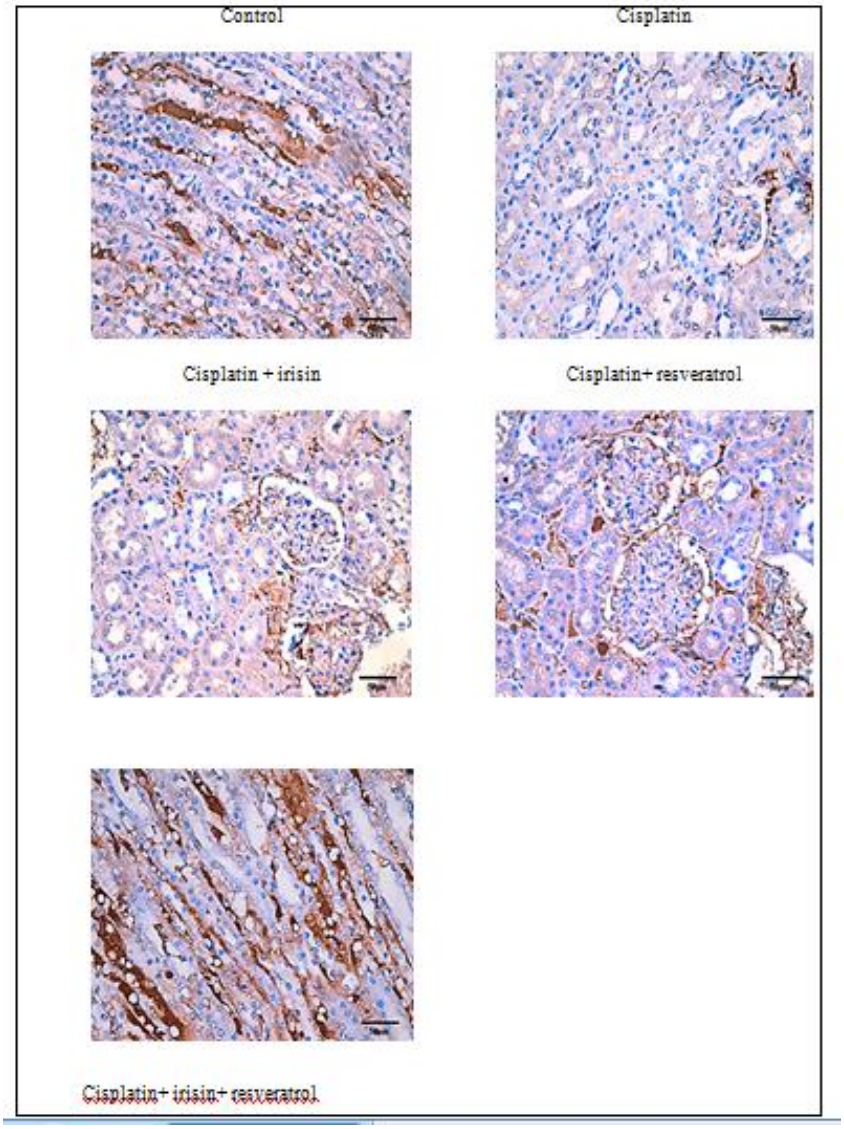


Fig.5: Histological pathological grading of renal injury using semi-quantitative scoring system from studied groups.



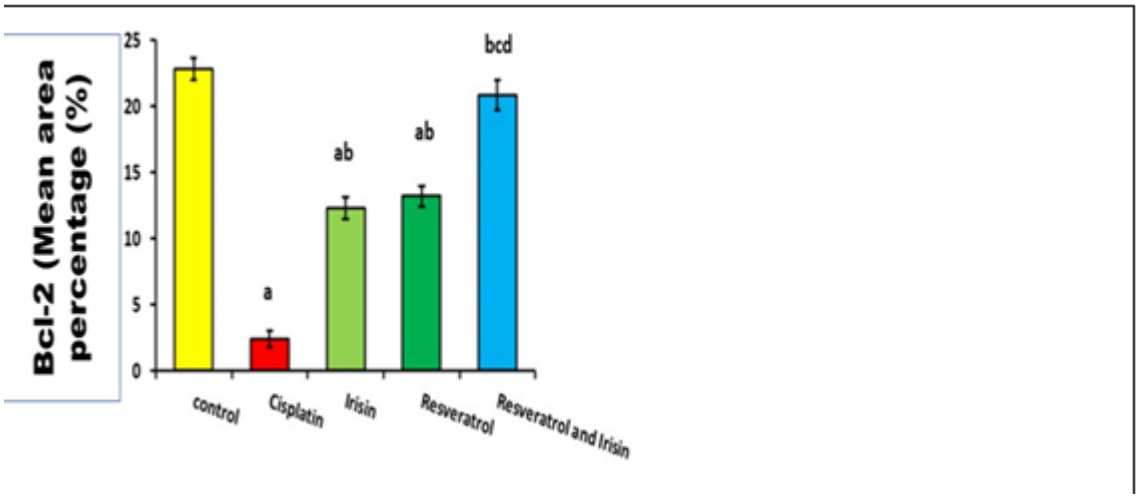


Fig. 6: The protective effect of irisin and resveratrol against cisplatin-induced renal damage was demonstrated by a photomicrograph of the rats' kidneys taken utilizing Bcl-2 immunostaining. The control group's cortex and medulla exhibited extensive tubular lining epithelium Bcl-2 immunostaining. The tubular lining epithelium in the cisplatin group's cortex and medulla revealed mild Bcl-2 immunostaining. In the Cisplatin + irisin and Cisplatin + resveratrol groups, the tubular lining epithelium in the brain and medulla indicated moderate Bcl-2 immunostaining. The tubular lining epithelium in the cortex and medulla of the cisplatin + irisin + resveratrol group showed extensive Bcl-2 immunostaining. Scale bar: 50 μm, original magnification: x400.Data are expressed as mean± SEM. Superscripts $^{a, b, c}$ and ^{d} denote a significant statistical difference at ($P < 0.05$). ^{a} $p<0.05$ Vs. Control I, ^{b} $p<0.05$ Vs Cis II, ^{c} $p<0.05$ Vs. irisin III, ^{d} $p<0.05$ Vs. Resveratrol IV by using One-way ANOVA and Tukey's post hoc test.

3. Discussion

Cisplatin is a well-known anticancer drug with two properties: first, it is mainly excreted in the kidneys and has a five-fold higher accumulation in the kidneys than in the blood; second, it is metabolized to a nephrotoxic metabolite. These two properties are mainly involved in the spoilage of kideny tubular cells and AKI caused by cisplatin[28-29]. AKI caused by cisplatin is distinguished with a complex set of events that include oxidative injury, inflammation, and an imbalance between autophagy and apoptosis[4].

Ferroptosis, formally defined in 2012, is an iron-dependent type of controlled cell death that depends on reactive oxygen species (ROS) apart from classical apoptosis, necrosis, and autophagy[30].Recently, several studies confirmed that ferroptosis played a cosiderable part in AKI caused by cisplatin which was confirmed by increased total and ferrous iron, and various metabolic markers of ferroptosis, involving excessive lipid peroxidation, and declined glutathione peroxidase 4 (GPX4) activity in vivo as well as in vitro[31-34].

MIOX, a proximal tubule-specific enzyme, aggravates renal oxidative-reductive injury in multiple disease states including AKI. Several pathways can be modulated in circumstances of MIOX overexpression to emphasize ferroptosis in AKI caused by cisplatin[31].

Nrf2 is a crucial element in preservation cellular redox equilibrium and cellular antioxidant response. The activation of Nrf2 or its target genes corrected the considerable increase in lipid peroxidation and ROS generation caused by cisplatin [32].

Therefore, based on what was explained in the previous lines, the untreated cisplatin group revealed a notable rise in renal index, serum

creatinine and BUN, renal MDA, TNFα, IL6, iron and MIOX in contrast to normal conrlol group. Even though there was a notable decline in renal GPX4 activity, GSH, Nrf2 exprsssion and the immunohistochemical exprsssion of the anti-apoptotic marker Bcl-2. Histopathological examination confirmed a shrunken glomerulus, wide Bowman's space, peritubular infiltration with inflammatory cells, interstitial hemorrhage, and dilatation of convoluted tubule lumens with vacuolated cytoplasm which agree with**Fahmy et al. 2024**[35].

Irisin is a multifunctional protein produced by skeletal muscles during excerise[36]. Numerous investigations have shown that irisin exerted antioxidant, anti-inflammatory, anti apoptotic properties in various conditions[8-10].But so far, according to our knowladge, there is no study that clarifies the role of irisin in cases of AKI by cisplatin and its link to the process ferroptosis.The irisin dose in the present study was administered, as described previously [19].

In this investigation irisin attenuating AKI caused by cisplatin demonstrated by notabledecerease in renal index, serum createnin and BUN leveles,as well as in the noticeable improvement in the histopathological examination as compared to untreeatd cisplatin group. These results aligned with earlier studies published by **Qiongyue et al**[37].

In the current study, treatment by irisin provided antioxidant effect as evidenced in the considerable decrease in MDA and significant rise in GSH in contrast to the cisplatin-untreated group and these results are consistent with earlier research which demonstrated the role of irisin in reducing oxidative injury and enhancing antioxidant status in different I/R models including cardiac, hepatic and renal tissues[38-40].

Furthermore, irisin treatment effectively reduces intracellular renal iron content, and increases the of GPX4 activity as compared to the untreated cisplatin group indicating that ferroptosis suppression may be linked with irisin's antioxidant properties as reported by**Zhang et al. (2021a)**[40] and **Qiongyue et al (2022)**[37].

Additionally, irisin therapy dramatically stopped the rise in inflammatory factors TNF-α and IL-6, which is coincided with **Jin et al (2020)**[41] who showed that antiinflammatory impact of irisn in AKI induced by sepsis suggested that the fundamental mechanism might be connected to nuclear factor-κB (NF-κB), because p65 and IκKα were upregulated while IκB-α was downregulated by irisin.

Moreover, **Qiongyue et al (2022)**[37] confirmed that irisin could protect and cure AKIcaused by sepsis in mice through activating the SIRT1/Nrf2 signaling pathway and suppressing ferroptosis and this represneted in our study by upregulation of Nrf2 expression downregualtion of MIOX expression as compared to untreated cisplatin group. In the current investigation, the considerable increase in Bcl-2 expression in irisin group relative to the cispaltin group further demonstrated the anti-apoptotic function of irisin, which was consistent with **Jin et al. (2020)**[41].

Resveratrol is a polyphenol famous by its antioxidant and anti-inflammatory actions [42], that was reported to produce valuble effects for a number of kidney morbidities involving diabetic nephropathy[43], AKI caused by sepsis[44] ,

reperfusion injury[45]as well as cispaltin renal damage[46-47].

In the meantime, resveratrol has been shown to have positive benefits against a number of chemotherapy induced organ toxicity through attenuating ferroptosis such asFluorouracil (5-FU)-induced cardiotoxicity[14-15]and Doxorubicin induced carditoxiccity[16].These results motivate us to look into whether resveratrol's beneficial effect on cisplatin-induced AKI was linked to reducing ferroptosis.

Because of its considerable intestinal conjugation and fast liver metabolism, resveratrol has almost no oral bioavailability. Oral-administration by gavage did not show any renal benefits. Therefore, based on earlier research using rat models of renal damage, the intraperitoneal route was selected[46].

In the current investigation, resveratrol successfully mitigated Cis-induced AKI as evidenced by the notable decline in renal index, serum creatinine and BUN, as well as in the improvement of histopathological analysis, as previously recorded by **DoAmaral et al (2008)**[46]and **Hao et al (2016)**[48].

In addition, resveratrol cuased a significant decrease in the intracellular renal iron content, ROS production & lipid perioxidation and MOIX exprssion, as well as a significant increase in GPX4 activity and Nrf2 expression suggesting that resveratrol efficaciously alleviated Cis-induced ferroptosis. These results coincided with earlier research published by **Li et al (2023)**[14]and **Chen et al (2024)**[16].

Consequently, resveratrol also markedly declined the generation of IL-6 and TNF-α, two pro-inflammatory cytokines, which is consistent with earlier research in sepsis-induced AKI published by**Luo et al (2020)**[49], who linked the ERS-IRE1-NF-κB pathway to the anti-inflammatory action of resveratrol.

Additionally, in our investigation, resveratrol upregulated Bcl 2 expression in contrast with the cisplatin group. This is consistent with **Hao et al (2016)**[48], who demonstrated that resveratrol could play a significant protective role in cispaltin induced AKI via inhibiting apoptotic pathways by reducing Bax expression and increasing Bcl 2 expression by means of caspase 8's interaction with intrinsic and extrinsic signaling pathways.

As far as we know, the current work was the first to demonstrate the benefits of irisin and resveratrol either alone or in combination against AKI's Cis-induced ferroptosis.

In our research, the co-administeration of irisin and resveratrol led to significant reduction of renal index, serum creatinine and BUN, intracelluar renal iron, lipid peroxidation, proinflamtory cytokines and MOIX expression.This was accompanied by a considerable increase in GPX4 activity, Nrf2 exprssion and Bcl-2 expression together with improved histopathologic picture, as opposed to using only one of these agents.

Conclusion

The beneficial effects of irisin and resveratrol combination in cisplatin-induced AKI model were more pronounced versus each agent alone. This might be as a result of the fact that each of these agents has effective antioxidant, anti-inflammatory and anti-apoptotic qualities besides their capacity to modulate ferroptosis.

Limitations of the study

The current study has possible limitations. The small number of Animals. Although this study showed additive protective effects of the combination of resveratrol with irisin, how each agent affected ferroptosis in the different manner remained unclear. Whether resveratrol and irisin directly affected ferroptosis process, or merely prevented oxidative stress leading to inhibition of ferroptosis. Probably, in vitro experiments are needed.To further analyze apoptosis, TUNEL labeling oralternatives such as pro-apoptotic factors were needed. Additionally, further research is required to determine the precise molecular pathways; unfortunately, this part of the current study was limited due to financial constraints.

Author contributions Conceptualization,Project administration,Writing- Original draft and supervision were performed by**Mayada Mohamed Ahmed Azab**. Visualization, Validation, Writing- Reviewing and Editingand supervision were performed by **Amr Zidan.** Writing- Original draft for pathology and IHC parts was performed by **Nancy Nagy Abd El-Hady**. Methodologyand Resourceswere performed by **Eman Sobhy Ahmed Abd Ellatif & Hadeer Shaker Salah**.Visualization and Writing-Reviewing and Editingwere performed by **HebatuallahAbedelhaleem Elhabiby**. Conceptualization, Project administration,Investigation, Data curation, Software and Formal analysis were performed by **Nesren Mohamed Mohamed**.Allauthors read and approved the final manuscript

Funding

This research did not receive any specific grant from funding agencies in the public, commercial or not-for-profit sectors.

Data availability statement

The datasets of the current study are available from the corresponding author on reasonable request

Declarations

Conflicts of interest: No conflict of interest.

Ethics approval: The study was approved by ethical approval code of 36264PR1007/12/24, the Animal Research Ethical Committee at Tanta University's Faculty of Medicine**,** Egypt**.**

Consent to participate

The study is not human based.

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