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Original article

Myrtenol Protects Against Acute Kidney Injury Induced by Cisplatin in Mice

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Abstract

Background and objectives: Cisplatin is an effective anticancer drug which has some side effects such as acute kidney injury. Myrtenol, a monoterpene alcohol which is found in some plants, has various pharmacological effects including anti-inflammatory and antioxidant activities. In this study, we evaluated the nephroprotective effects of myrtenol in acute kidney injury induced by cisplatin in male mice. **Methods:** In this experimental in-vivo study, 35 male mice were randomly separated into 5 groups, including control, CIS (20 mg/kg cisplatin, intraperitoneally on day 1), dimethyl sulfoxide (DMSO; received cisplatin only on day 1, plus DMSO 1% on the first day, continued for 3 days), and treatment groups (received cisplatin only on day 1, plus myrtenol 25 mg/kg and 50 mg/kg intraperitoneally on the first day, continued for 3 days). The blood urea nitrogen (BUN) levels were evaluated in serum. The renal tissues were collected for evaluating malondialdehyde (MDA), superoxide dismutase (SOD), and catalase (CAT) activities; histopathological investigation was also performed. **Results:** Our results showed that cisplatin administration caused significant elevation in the levels of renal MDA and serum BUN; in contrast, renal SOD and CAT activities significantly reduced. Myrtenol treatment, especially 50 mg/kg for four consecutive days mitigated these alternations in serum and renal tissue. Also, the kidney's histopathological investigations were consistent with biochemical and oxidative parameters. **Conclusion:** The results of our study revealed that myrtenol ameliorates acute kidney injury induced by cisplatin via oxidative stress suppression.

Keywords: cisplatin; kidney; myrtenol; oxidative stress

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Introduction

Cisplatin is a simple inorganic platinum-based molecule that binds to DNA and inhibits DNA synthesis and replication of DNA [1]. Cisplatin is an antineoplastic agent that is widely used in the treatment of various types of solid tumor neoplasms [2]. One of the most frequent side effects of cisplatin-based chemotherapy is acute kidney injury, which limits the clinical usage of this drug [3, 4]. Although some factors have been identified for the pathophysiology of acute kidney injury induced by cisplatin, the exact pathogenesis remains unknown; this leads to a lack of effective treatment for inhibiting these side effects [5]. The most important factors involved include oxidative stress and inflammation [5,6]. It is well established that cisplatin accumulates in renal tubules and increases the production of reactive oxygen species (ROS) in renal tissue, which leads to lipid peroxidation of the membrane. On the other hand, the overproduction of ROS inhibits the enzymatic and/or non-enzymatic components of antioxidant defense systems in the kidney [7-9].

Previous evidence has shown the beneficial usage of natural products for the mitigation of acute kidney injury induced by cisplatin [7,10]. Myrtle

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(*Myrtus communis* Linn.) as a medicinal plant is used in traditional medicine and for the first time Datta et al., explain about the pharmacognosy of this plant [11]. This plant is widely distributed in Africa, Europe, and Asia [12-14]. Myrtenol (monoterpene alcohol), as one of the components of myrtle, has various pharmacological and therapeutic properties, including anticancer [15], antinociceptive [16], neuroprotective [17], anti-hyperglycemic [18], anti-inflammatory [19], and antioxidant activities [18,20]. It has been demonstrated that myrtenol has direct antioxidant properties through the removal of free ROS and inhibition of lipid peroxidation [21]. On the other hand, this agent indirectly reduces the oxidative status via increasing the antioxidant enzymes such as superoxide dismutase (SOD) and catalase (CAT) [18]. Myrtenol has beneficial effects on cardiac ischemia through the reduction of oxidative stress and suppression of the pro-apoptotic pathway [22]. Recently, it has been shown that myrtenol inhalation reduces anxiety-like behaviors and cognitive deficits in asthmatic rats via decreasing the levels of interleukin-6, interleukin-17, tumor necrosis factor-α, and malondialdehyde (MDA) in the hippocampus [23].

Regarding the fact that cisplatin induces nephrotoxicity through increasing the oxidative stress in kidney tissue and considering the high antioxidative and anti-inflammatory effects of myrtenol, we aimed to evaluate the effect of myrtenol on acute kidney injury induced by cisplatin in mice by studying oxidative stress biomarkers and pathological changes because no research has been conducted about the nephroprotective effects of myrtenol yet.

Material and Methods

Ethical considerations

All experimental procedures were approved by the ethical committee of Kerman University of Medical Sciences (Ethics code: IR.KMU.REC.1400.061) and were in accordance with the National Institutes of Health Guide for the Care and Use of Laboratory Animals (NIH Publications, Eighth edition).

Chemicals

Myrtenol and dimethyl sulfoxide (DMSO) were purchased from the Sigma-Aldrich Co. (Germany). Cisplatin was purchased from MYLAN Co. (France). Kits for estimating the serum BUN and Cr levels were purchased from Pars Azmoon Co. (Iran). Moreover, kits for estimating the SOD and CAT activities were purchased from the Randox Co. (Randox Laboratories Ltd., UK).

Animals and experimental design

In this experimental in vivo study, 35 male mice (weight: 28±1 g; age: 24 weeks) were purchased from the animal house of Kerman University of Medical Sciences, Kerman, Iran. The Animals were housed under controlled conditions (22±2 °C and 12-12 h light/dark cycle) with free access to drinking water and standard rodent chow (Pars Industrial Company, Iran).

The animals were weighed and randomly separated into five groups (n=7/group) as follows: (1) control group (CON; received no intervention), (2) CIS group (CIS; received intraperitoneal injection of 20 mg/kg cisplatin only on day 1), (3) DMSO group (DMSO; received intraperitoneal injection of 20 mg/kg of cisplatin only on day 1, plus DMSO 1% on the first day, continued for 3 days), (4 and 5) treatment groups (cisplatin+Myrtenol 25 and cisplatin+Myrtenol 50; received intraperitoneal injection of 20 mg/kg of cisplatin only on day 1, plus myrtenol 25 mg/kg and 50 mg/kg intraperitoneal on the first day, continued for 3 days).

Myrtenol was dissolved in DMSO 1%. The route of administration and doses were selected from previous reports [5,24,25].

Sample collection

On day 5 of the experiment, the animals were weighed and anesthetized. After that, blood samples were obtained from the orbital sinus. To measure blood urea nitrogen (BUN) and creatinine (Cr) levels, serums were separated through centrifugation at 1000 rpm for 3 min and kept at -20 °C. The animals were killed by rapid decapitation. Immediately, both kidney tissues were harvested and washed with ice-cold saline. The right kidney was preserved in a 10% formalin solution for histopathological studies. The left kidney was frozen by using liquid nitrogen for investigation of the oxidative stress parameters [26].

Serum parameters

Serum BUN and Cr were estimated using the Selectra-XLbiochemical autoanalyzer (Vital

Science, the Netherlands) according the manufacturer guild lines.

Oxidative parameters

Phosphate-buffered saline was used to homogenize the frozen kidneys after defrosting them. Supernatants were collected through centrifugation at 6000 rpm for 25 minutes at 4 ℃ [27, 28]. After that, SOD and CAT activities and MDA levels were assessed in the removed supernatants as follows.

MDA was measured as the lipid peroxidation index. It reacts with thiobarbituric acid at high temperatures to produce a pink-colored product that was assessed by the colorimetric method at 540 nm [29].

SOD activity was evaluated based on kit protocol. This enzyme converts superoxide (O_2-·) to hydrogen peroxide (H_2O_2) and molecular oxygen (O_2). In this kit, O_2- ions produce H_2O_2 through the activity of xanthine oxidase and the conversion of xanthine to uric acid. SOD reduces the production of NBT-deformazan by reducing O_2-ion ions, which measures SOD activity at 560 nm [30].

The activity of CAT was measured by using the commercial colorimetric assay according to the kit guideline. The absorbance was recorded at 570 nm.

Pathological assessments

For pathological investigation, the fixed kidneys were dehydrated by absolute ethanol solution and embedded in paraffin; the samples were sliced at 5 μm thickness. afterward, sections were stained by using hematoxylin and eosin (H&E) and observed under a light microscope (Nikon Labophot, Japan) [31]. All slides were evaluated blindly by a pathologist for pathological lesions including inflammation, necrosis, congestion, and cast. Each parameter severity was scored by a semiquantitative method into 4 categories: normal: 1, mild: 2, moderate: 3, and severe: 4. At last, the average of each slide was reported.

Statistical analysis

Data were analyzed using GraphPad Prism (version 6, USA). The data were given as mean ± SD. We used the Kolmogorov–Smirnov test to find out whether our data had normal distribution. For parametric variables, the differences between the groups were defined using one-way ANOVA followed by Tukey's post hoc test. For non-parametric variables, we used the Kruskal-Wallis test followed by Dunn's post hoc analysis. Statistical significance was set at $p< 0.05$.

Results and Discussion

Our results showed that intraperitoneal administration of cisplatin (20 mg/kg) led to acute kidney injury as manifested by an increase in the serum level of BUN and Cr. Moreover, the results of histopathological investigations and oxidative parameters were compatible with changes in renal function. It was also observed that intraperitoneal administration of myrtenol (50 mg/kg) attenuated acute kidney injury in the cisplatin-administered animals by reducing serum BUN concentration and renal MDA levels as well as increasing the activities of renal CAT and SOD. Furthermore, treatment with myrtenol significantly mitigated the extensive lesions in renal tissue induced by cisplatin including tubular inflammation, congestion, necrosis, and cast. We did not find any difference in the mean body weight of different experimental groups on day 1 (Figure 1). The mean body weight significantly decreased in cisplatin- and DMSO-administered mice compared with the CON group on day 5 ($p<0.05$). Treatment with myrtenol at the dose of 50 mg/kg significantly improved the body weight in cisplatin-treated animals on day 5 ($p< 0.05$).

The mean level of serum BUN significantly increased in cisplatin and DMSO groups compared with the CON group ($p<0.001$ and $p<0.01$, respectively) (Figure 2A). Treatment with myrtenol at the dose of 50 mg/kg significantly decreased the BUN levels in cisplatin-treated animals ($p<0.05$). Furthermore, the mean level of serum Cr significantly increased in mice of cisplatin and DMSO groups compared with the CON group ($p<0.05$) (Figure 2B). Animals treated with 50 mg/kg of myrtenol showed a significant decrease in Cr levels compared with the cisplatin group ($p<0.05$). Cisplatin stimulated ROS production in the kidney tissue which led to tissue injuries and a rise in the BUN and Cr levels [5,32]. Aligned with past studies, the results of the current study indicated that intraperitoneal administration of cisplatin increases serum BUN and Cr levels. Furthermore, it was observed that treatment with myrtenol decreased serum BUN and Cr levels in cisplatin-administrated mice. Previous studies have revealed that substances with antioxidant activities such as calcium dobesilate, ellagic acid,

and lycopene can improve functional disorders of acute kidney injury induced by cisplatin via attenuation of oxidative stress and alleviation of serum BUN and Cr levels [25,33,34]. It has been confirmed that myrtenol has potent antioxidative properties via direct suppression of ROS production [20,22]. Hence, myrtenol may show its nephroprotective effects through the abatement of renal oxidative stress. Figure 3A illustrates the effect of myrtenol on the concentration of MDA in renal tissue. As shown, cisplatin administration (alone or with DMSO) significantly increased the level of MDA ($p<0.01$ and $p<0.05$, respectively) compared with the CON group. Treatment with myrtenol (50 mg/kg) for four consecutive days significantly reduced MDA concentration in cisplatin-administered mice. According to our findings, the activity of antioxidant enzymes, including CAT and SOD significantly decreased in the CIS- and DMSO-administered animals in comparison with the CON animals (for CAT: $p<0.01$ and $p<0.05$; for SOD: $p<0.001$) (Figure 3B, C). Administration of myrtenol (50 mg/kg) for four constitutive days in cisplatin-administered mice caused a significant rise in the mentioned antioxidative indices when compared with the CIS group ($p<0.05$). It is well established that oxidative stress has a fundamental role in cisplatin-induced acute kidney injury which is accompanied by an increment of MDA level and a decrease of SOD and CAT activities in renal tissue [2,35]. Also, we noticed that myrtenol significantly attenuated these changes in the renal tissue of cisplatin-administrated animals. In return, compounds and natural products with antioxidant properties manifested protective effects against nephrotoxicity [7,36,37]. Xuemei et al. found that myrtenol administration (50 mg/kg) considerably mitigated MDA and increased the activity of antioxidant enzymes such as CAT, SOD, and glutathione peroxidase in the liver tissues of diabetic rats [38]. Moreover, myrtenol suppresses the MDA increase in the stomach tissue through its antioxidant properties [39].

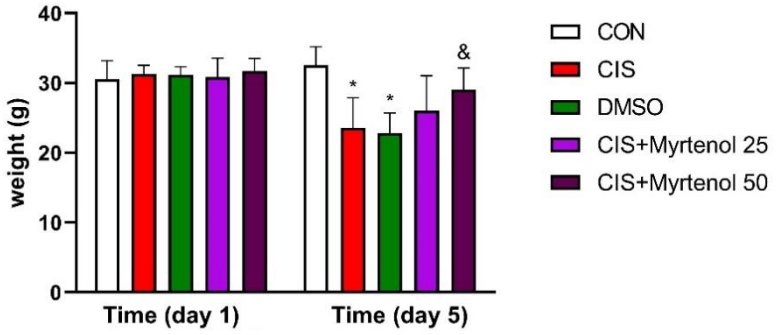

Figure 1. The Effect of myrtenol on body weight on days 1 and 5 in cisplatin-induced acute kidney injury. Data are expressed as mean ± SD. *: significant difference compared with the CON group (*$p<0.05$); &: significant difference compared with the CIS group (&: $p<0.05$); CON: control; CIS: cisplatin; DMSO: dimethyl sulfoxide in saline (1%); CIS+myrtenol 25: cisplatin plus myrtenol 25 mg/kg; CIS+myrtenol 50: cisplatin plus myrtenol 50 mg/kg

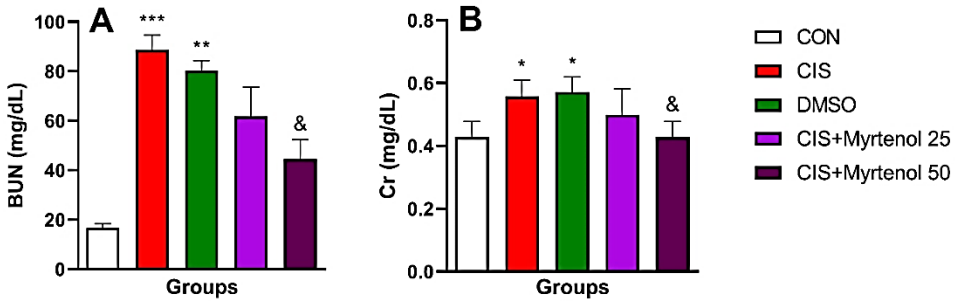

Figure 2. The Effect of myrtenol on serum BUN (A) and Cr (B) levels in cisplatin-induced acute kidney injury. Data are expressed as mean ± SD. *: significant difference compared with the CON group (*$p<0.05$, **$p<0.01$ and ***$p<0.001$; &: significant difference compared with the CIS group (&: $p<0.05$); CON: control; CIS: cisplatin; DMSO: dimethyl sulfoxide in saline (1%); CIS+myrtenol 25: cisplatin plus myrtenol 25 mg/kg; CIS+myrtenol 50: cisplatin plus myrtenol 50 mg/kg

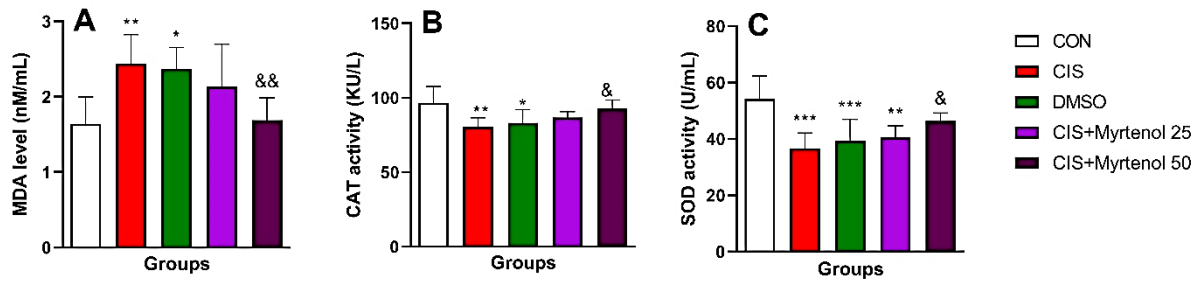

Figure 3. The Effect of myrtenol on renal MDA level (A), CAT activity (B), and SOD activity (C) in cisplatin-induced acute kidney injury. Data are expressed as mean ± SD. *: significant difference compared with the CON group ($^{*}p<0.05$, $^{**}p<0.01$ and $^{***}p<0.001$); &: significant difference compared with the CIS group (&: $p<0.05$ and &&: $p< 0.01$); CON: control; CIS: cisplatin; DMSO: dimethyl sulfoxide in saline (1%); CIS+myrtenol 25: cisplatin plus myrtenol 25 mg/kg; CIS+myrtenol 50: cisplatin plus myrtenol 50 mg/kg

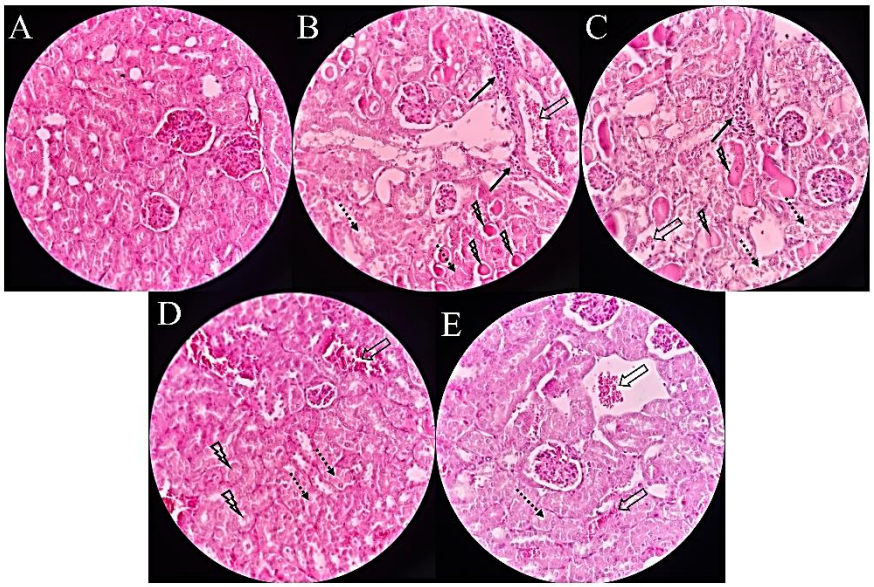

Figure 4. The effects of myrtenol on renal tissue changes in cisplatin-induced acute kidney injury (H&E staining, magnification X 400). (A) CON group; (B) CIS group; (C) DMSO group; (D) CIS+myrtenol 25 group; (E) CIS+myrtenol 50 group; inflammation (black arrow), congestion (hollow arrow), necrosis (dotted arrow), cast (lightning bolt); CON: control; CIS: cisplatin; DMSO: dimethyl sulfoxide in saline (1%); CIS+myrtenol 25: cisplatin plus myrtenol 25 mg/kg; CIS+myrtenol 50: cisplatin plus myrtenol 50 mg/kg

Furthermore, myrtenol exerts its cardioprotective effects in myocardial ischemia-reperfusion injury models by preventing the increase in oxidative stress parameters such as hydroperoxide levels and ROS [22]. A report has suggested that myrtenol attenuates inflammation by mitigating lipid peroxidation and enhancing SOD activity [20]. In an experimental study, it was revealed that myrtenol reduced the inflammatory markers leading to the enhancement of antioxidant status in diabetic animals [38]. According to the mentioned studies, myrtenol may ameliorate cisplatin-induced acute kidney injury by reducing lipid peroxidation and enhancing the activity of the antioxidant defense system.

Figures 4 and 5 illustrate the results of renal histopathology experiments. The renal tissues of the CON group displayed normal kidney morphology (Figures 4A and 5). The renal tissues of cisplatin- and DMSO-administrated animals displayed extensive lesions including inflammation, congestion, necrosis, and cast

($p<0.001$ except congestion in DMSO-administrated animals with $p<0.01$) (Figures 4B, C and Figure 5). Myrtenol (50 mg/kg) effectively improved all the pathological changes induced by cisplatin (inflammation, congestion, and necrosis: $p<0.05$; for the cast: $p<0.01$) (Figures 4E and 5). Acute kidney injury is essentially due to accumulation of cisplatin in the proximal and distal tubules.

This accumulation results in reduction of renal blood flow and a decline in glomerular filtration rate, leading to the destruction and necrosis of renal tubular epithelial cells and stimulation of oxidative stress [7]. Our histopathological assessments are in line with the previous investigations and parallel with our biochemical and oxidative parameters [5,40,41]. Microscopic explorations in the cisplatin group showed intensive tubular necrosis, tubular inflammation, congestion, and cast. In addition, the nephroprotective properties of myrtenol were characterized by histopathological evaluation of kidney samples which implies remarkable amelioration of these lesions in the cisplatin-administrated animals. In line with our study, myrtenol significantly attenuated pathological lesions in hepatic and pancreatic tissues of diabetic rats via reduction of oxidative stress in hepatic tissue [38].

To the best of our knowledge, this is the first study about the nephroprotective effects of myrtenol. On the other hand, the current study has some limitations which originated from financial restrictions and limited us from measuring other pathways such as inflammation parameters to reveal the precise protective effect.

Conclusions

Our investigation suggested that cisplatin causes acute kidney injury by oxidative stress-induced damage. Treatment with myrtenol protects against cisplatin-induced acute kidney injury. This may be due to the antioxidant effects. Therefore, these results indicate that the administration of myrtenol could be a potential strategy for ameliorating cisplatin-induced acute kidney injury. Further studies are recommended to identify the accurate molecular mechanisms of myrtenol on cisplatin-induced acute kidney injury.

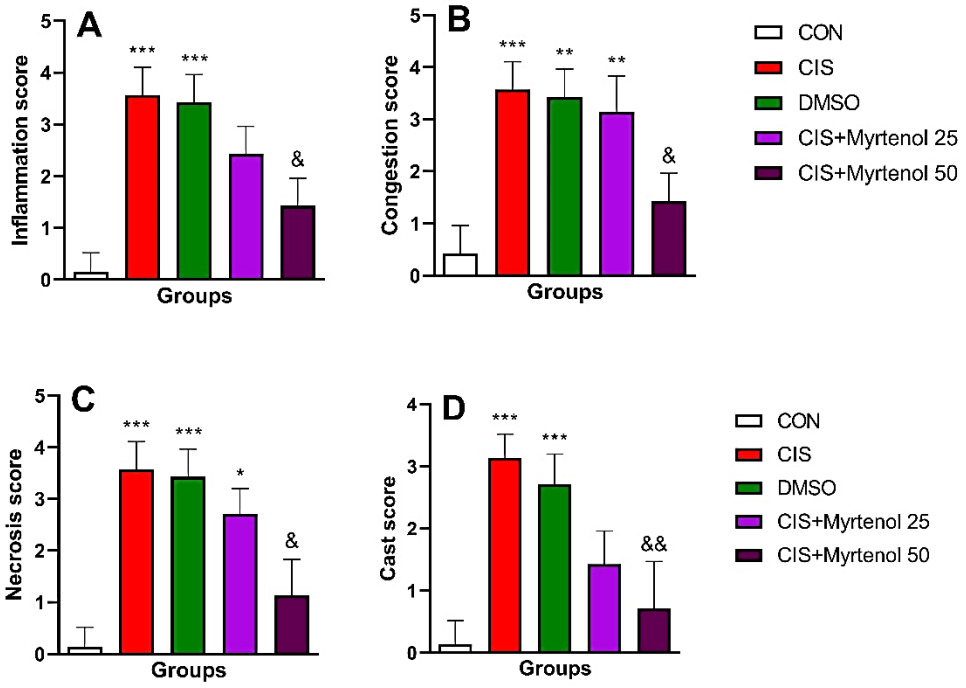

Figure 5. Effect of myrtenol on the pathological scores in cisplatin-induced acute kidney injury. (A) inflammation; (B) congestion; (C) necrosis; (D) cast. Data are expressed as mean ± SD. *: significant difference compared with the CON group ($^{*}p<0.05$, $^{**}p<0.01$ and $^{***}p<0.001$); &: significant difference compared with the CIS group (&: $p<0.05$ and &&: $p<0.01$); CON: control; CIS: cisplatin; DMSO: dimethyl sulfoxide in saline (1%); CIS+myrtenol 25: cisplatin plus myrtenol 25 mg/kg; CIS+myrtenol 50: cisplatin plus myrtenol 50 mg/kg

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Author contributions

Morteza Amirteimoury contributed in investigation, methodology, project administration, resources, funding acquisition and writing original draft; Iman Fatemi contributed in conceptualization, data curation, formal analysis, funding acquisition, software, supervision, validation, visualization, reviewing and editing.

Declaration of interest

The authors declare that there is no conflict of interest. The authors alone are responsible for the accuracy and integrity of the paper content.

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Abbreviations

BUN: blood urea nitrogen; CAT: catalase; CIS: cisplatin; CIS+myrtenol 25: cisplatin plus myrtenol 25 mg/kg; CIS+myrtenol 50: cisplatin plus myrtenol 50 mg/kg; CON: control; Cr: creatinine; DMSO: dimethyl sulfoxide; MDA: malondialdehyde; SOD: superoxide dismutase; ROS: reactive oxygen species