Dihydromyricetin Inhibits Ferroptosis to Attenuate Cisplatin-Induced Muscle Atrophy

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Summary

Cisplatin is a widely used chemotherapy drug for the treatment of various cancers. However, although cisplatin is effective in targeting cancer cells, it has severe side effects including skeletal muscle atrophy. In this study, we aimed to characterize the role of Dihydromyricetin in cisplatin-induced muscle atrophy in mice. 5-week-old male C57BL/6 mice were treated with Dihydromyricetin for 14 days orally followed by in intraperitoneally cisplatin administration for 6 days. Gastrocnemius muscles were isolated for the following experiments. Antioxidative stress were determined by peroxidative product malondialdehyde (MDA) and antioxidants superoxide dismutase (SOD) and glutathione peroxidase (GPx) activities. Quadriceps muscle mass and grip strength were significantly restored by Dihydromyricetin in a dose-dependent manner. Moreover, muscle fibers were improved in Dihydromyricetin treated group. Excessive skeletal muscle E3 ubiquitin-protein ligases in cisplatin group were significantly repressed by Dihydromyricetin treatment. Dihydromyricetin significantly reduced oxidative stress induced by cisplatin by decreasing MDA level and restored SOD and GPx activities. In addition, ferroptosis was significantly reduced by Dihydromyricetin characterized by reduced iron level and ferritin heavy chain 1 and improved Gpx4 level. The present study demonstrated that Dihydromyricetin attenuated cisplatin-induced muscle atrophy by reducing skeletal muscle E3 ubiquitin-protein ligases, oxidative stress, and ferroptosis.

Key words

Dihydromyricetin • Cisplatin-induced muscle atrophy • Oxidative stress • Ferroptosis

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Introduction

Muscle atrophy is characterized by a decrease in muscle mass due to aging, malnutrition, illness states, immobility [1]. Chemotherapy is the use of anticancer drugs according to a standardized treatment regimen for various types of cancer [2]. Cisplatin, a platinum-based anticancer drug, is widely used in the treatment of tumors such as cervical, head and neck, breast, and ovarian cancers, etc. [3,4]. Cisplatin induces apoptosis by inhibiting DNA synthesis. Although cisplatin is effective in inhibiting tumor cells proliferating, it is also associated with many side effects, including nausea, weight loss, muscle atrophy, fatigue, and dysfunction, which are considered hallmarks of cachexia and sarcopenia, which in turn significantly affect the outcome of treatment [5,6].

Dihydromyricetin is the main bioactive polyphenol in *Garcinia cambogia*. *Garcinia cambogi*a has been used as an anti-inflammatory agent for centuries in China and other Asian countries. Dihydromyricetin exerts anti-inflammatory effects by inhibiting the macrophage nuclear factor kappa-B signaling pathway [7]. Moreover, Dihydromyricetin improves physical performance at high altitude by maintaining mitochondrial biogenesis in skeletal muscle [8]. It has been shown that Dihydromyricetin prevents insulin resistance in skeletal muscle by inducing autophagy [9].

Xu *et al.* reported that Dihydromyricetin attenuates cisplatin-induced acute kidney injury by reducing oxidative stress, inflammation and ferroptosis [10,11]. These data suggest that Dihydromyricetin ameliorates cisplatin-induced organ injury and inhibited ferroptosis. Ferroptosis has been reported to be associated with cisplatin-induced muscle atrophy. It has shown that Dihydromyricetin resists inflammation-induced muscle atrophy *via* ryanodine receptor-calmodulin-dependent protein kinase kinase (CaMKK)-Adenosine 5'-monophosphate (AMP)-activated protein kinase (AMPK) signal pathway [8]. Therefore, the aim of the present work was to investigate whether Dihydromyricetin has an attenuating effect on muscle atrophy in an animal model of cisplatin-induced muscle atrophy and whether ferroptosis is involved.

Methods

Animal model

5-week-old male C57BL/6 mice were purchased from SLAC Laboratory Animal Co., Ltd. (Shanghai, China). Mice were husbanded in a climate- controlled environment with a 12-h light/dark cycle, access to water and standard rodent food. The presented study was approved by the Institute Animal Care and Ethics Committee of the Second Affiliated Hospital, Hengyang Medical School, University of South China.

Mice were divided into three groups: control group (same volume of phosphate-buffered saline), Cisplatin group (200 µl of 3 mg/kg body weight cisplatin intraperitoneally (i.p.)), Cisplatin-Dihydromyricetin (DHM) group (200 µl of 50, 100, 200 mg/kg body weight Dihydromyricetin once a day for 14 days, then combined with 200 µl Cisplatin (3 mg/kg body weight, i.p., for 6 days)).

Haematoxylin-eosin (HE) staining

Mice gastrocnemius muscles were fixed in 4 % paraformaldehyde solution. Then, fixed tissues were embedded in paraffin and cut into 4 µM thick sections and stained using H&E staining kit (G1121, Solarbio). The sections were assessed and analyzed using Cellsens software.

Grip strength measurement

On day 20, grip strength was measured using a grip strength meter (SH-20, NSCING, Nanjing, China). Mice were placed on a metal mesh that they could hold with their two forelimbs. Each mouse's tail was pulled three times parallel to the metal mesh. In order to represent muscular force, the greatest force value was used during the grasp procedure.

Western blot analysis

Total protein from gastrocnemius muscles were extracted using radioimmunoprecipitation assay buffer (89900, Thermo Fisher Scientific, Massachusetts) containing protease inhibitor (P0100, Solarbio) and phosphatase inhibitor (4906837001, Roche, Basel, Swiss). Proteins were loaded on to sodium dodecyl sulfate–polyacrylamide gel electrophoresis gel. Then blots were transferred to polyvinylidene fluoride membranes and blocked in 5 % bovine serum albumin or 5 % non-fat milk at room temperature for 1 h. The blots were incubated with primary antibodies against muscle RING-finger protein 1 (MuRF1) and muscle atrophy F-box (Atrogin-1), ferritin heavy chain 1 (Fth1), glutathione peroxidase (Gpx) 4, and glyceraldehyde-3-phosphate dehydrogenase (GAPDH) in the cold room overnight. Then blots were incubated with secondary antibodies at room temperature for 1 h. The protein levels were visualized using Cellsens software (Olympus Corporation, Tokyo, Japan).

RNA isolation and quantitative real-time polymerase chain reaction (qRT-PCR)

Total RNA was isolated from the gastrocnemius muscles using RNAsio Plus (9109, Takara, Kyoto, Japan) according to the manufacturer's protocol. Complementary DNA (cDNA) was synthesized from 2000 ng total RNA with the HiScript II Q Select RT SuperMix (R223-01, Vazyme, Nanjing, China). qRT-PCR was performed using a reaction mixture containing SYBR Green master mix (Q711-02-AA, Vazyme). Results were calculated using the $2^{-\Delta\Delta CT}$ relative quantification method normalized to the GAPDH gene. The sequences of the primer pairs (5'-3') are shown as below: Fth1: Forward CAAGTGCGCCAGAACTACCA, Reverse ACAGATAGACGTAGGAGGCATAC; Gpx4: Forward GCAACCAGTTTGGGAGGCAGGAG, Reverse CCTCCATGGGACCATAGCGCTTC; GAPDH: Forward AATGGATTTGGACGCATTGGT, Reverse TTTGCACTGGTACGTGTTGAT; Myosin heavy chain 2 (Myh2): Forward GCGACAGACACCTCCTTCAAGAAC, Reverse GTCCAGCCAGCCAGTGATGTTG; Myosin heavy chain 4 (Myh4): Forward TGATGCAGGCTGAGATCGAGGAG, Reverse TTGGTGTTG-

ATGAGGCTGGTGTTC; Myosin heavy chain 7 (Myh7): Forward GCAAGACGGTGACTGTGAAGGAG, Reverse GGTTGACGGTGACGCAGAAGAG; MuRF1: Forward ACACAACCTCTGCCGGAAGT, Reverse ACGGAAACGACCTCCAGACA; Atrogin-1: Forward AGAAAAGCGGCAGCTTCGT, Reverse GCTGCG-ACGTCGTAGTTCAG.

Statistical analysis

Statistical analysis was performed by GraphPad Prism (v8.3) software (GraphPad Software Inc., San Diego, California). Data were represented as mean ± standard deviation (SD). $p<0.05$ was considered statistically significant. For comparison of three or more sets of measurements, one-way analysis of variance (ANOVA) followed Dunn's multiple comparisons test was performed.

Ethical approval

The presented study was approved by the Institute Animal Care and Ethics Committee of the Second Affiliated Hospital, Hengyang Medical School, University of South China. This study was performed in strict accordance with the NIH guidelines for the care and use of laboratory animals (NIH Publication No. 85-23 Rev. 1985).

Results

The effects of Dihydromyricetin on cisplatin-induced muscle atrophy in vivo

To evaluate whether Dihydromyricetin affected cisplatin-induced muscle atrophy *in vivo*. We treated mice with Dihydromyricetin for consecutively 14 days at different dose (50, 100, 200 mg/kg body weight, once a day). After 14 days while giving Dihydromyricetin, cisplatin (3 mg/kg body weight) were administrated to mice for consecutively 6 days. As shown in Figure 1A, B, in the first two weeks, in all groups body weights were increased, indicating the safety of Dihydromyricetin. After 14 days, body weights started to reduce in animals in cisplatin group. Notably, Dihydromyricetin treatment attenuated body weight loss induced by cisplatin (Fig. 1A, B). Quadriceps muscle mass also significantly reduced in cisplatin group when compared with the control group (Fig. 1C), whereas Dihydromyricetin treatment restored quadriceps muscle mass in a dose-dependent manner (Fig. 1C). In parallel, Grip strength were significantly reduced in cisplatin and successfully restored by Dihydromyricetin (Fig. 1D). To avoid waste of animals, we chose 200 mg/kg body weight of Dihydromyricetin for the following experiments. Together, these data indicated that Dihydromyricetin could attenuate cisplatin-induced muscle atrophy in mice.

The effects of Dihydromyricetin on the cross-sectional area (CSA) of muscle fibers from mice after cisplatin treatment

To further evaluate the effects of Dihydromyricetin on the CSA of muscle fibers, gastrocnemius muscles were sectioned and stained for H&E. As shown in Figure 2A, Dihydromyricetin treatment restored the muscle loss induced by cisplatin. Muscle fibers express different Myh2, Myh4 and Myh7. We measured the mRNA level in gastrocnemius muscles. Data showed that Cisplatin significantly reduced all Myh2, Myh4 mRNA levels, which were restored by the treatment of Dihydromyricetin (Fig. 2B-D). However, Cisplatin did not significantly affect Myh7 mRNA level.

The effects of Dihydromyricetin on the expressions of MuRF1 and Atrogin-1 in muscles from mice after cisplatin treatment

MuRF1 and atrophy gene-1/muscle atrophy F-box (Atrogin-1/MAFbx) are muscle-specific ubiquitin E3-ligases. It has been shown that these ubiquitin E3-ligases are essential for skeletal muscle cells protein degradation. In the present data, we found that the mRNA levels of MuRF1 and Atrogin-1 significantly elevated in cisplatin treated group relative to the control group (Fig. 3A, B). In contrast, treatment with Dihydromyricetin dramatically reduced the elevation of both MuRF1 and Atrogin-1 mRNA levels (Fig. 3A, B). Correspondingly, protein levels of MuRF1 and Atrogin-1 were reduced by the treatment of Dihydromyricetin (Fig. 3C-E).

The effects of Dihydromyricetin on cisplatin-induced oxidative stress in mice

In order to evaluate the effects of Dihydromyricetin on cisplatin-induced oxidative stress, we measured oxidative marker malondialdehyde (MDA) and antioxidants GPx and superoxide dismutase (SOD) activities. We found that MDA level was significantly increased, whereas GPx activity and SOD activity were decreased by cisplatin (Fig. 4A-C). Dihydromyricetin treatment significantly reduced oxidative stress, indicated by reduced MDA level and restored GPx and SOD activities (Fig. 4A-C). Together, these data suggested that Dihydromyricetin successfully inhibited cisplatin-induced oxidative stress in mice.

The effects of Dihydromyricetin on cisplatin-induced ferroptosis in mice

It has been shown that cisplatin-induced muscle atrophy is associated with ferroptosis. To assess whether Dihydromyricetin affects cisplatin-induced ferroptosis in mice, we measured iron level. As shown in Figure 5A, iron level was significantly elevated in cisplatin-treated group when compared with the control group. In the Dihydromyricetin-treated group, iron level was remarkedly reduced to that of control. In parallel, the increased mRNA level of Fth1 induced by cisplatin was reduced by the treatment of Dihydromyricetin (Fig. 5B). Moreover, a decrease in Gpx4 mRNA level was observed in cisplatin group, and Dihydromyricetin restored Gpx4 mRNA level significantly (Fig. 5C). Same trends were observed in terms of protein levels of Fth1 and Gpx3 (Fig. 5D-F). Overall, these data suggest that Dihydromyricetin rescued mice from cisplatin-induced ferroptosis.

Discussion

Cisplatin is a commonly used anti-cancer reagent, which is associated with side effects including muscle atrophy in patients. Muscle atrophy is characterized by muscle mass loss and dysfunction caused by elevation of muscle protein degradation and reduction of protein synthesis. Dihydromyricetin is a flavonoid compound found in plants such as *Ampelopsis grossedentata* (also known as “Ampelopsin” or “Myricetin-3-O-glucuronide”).

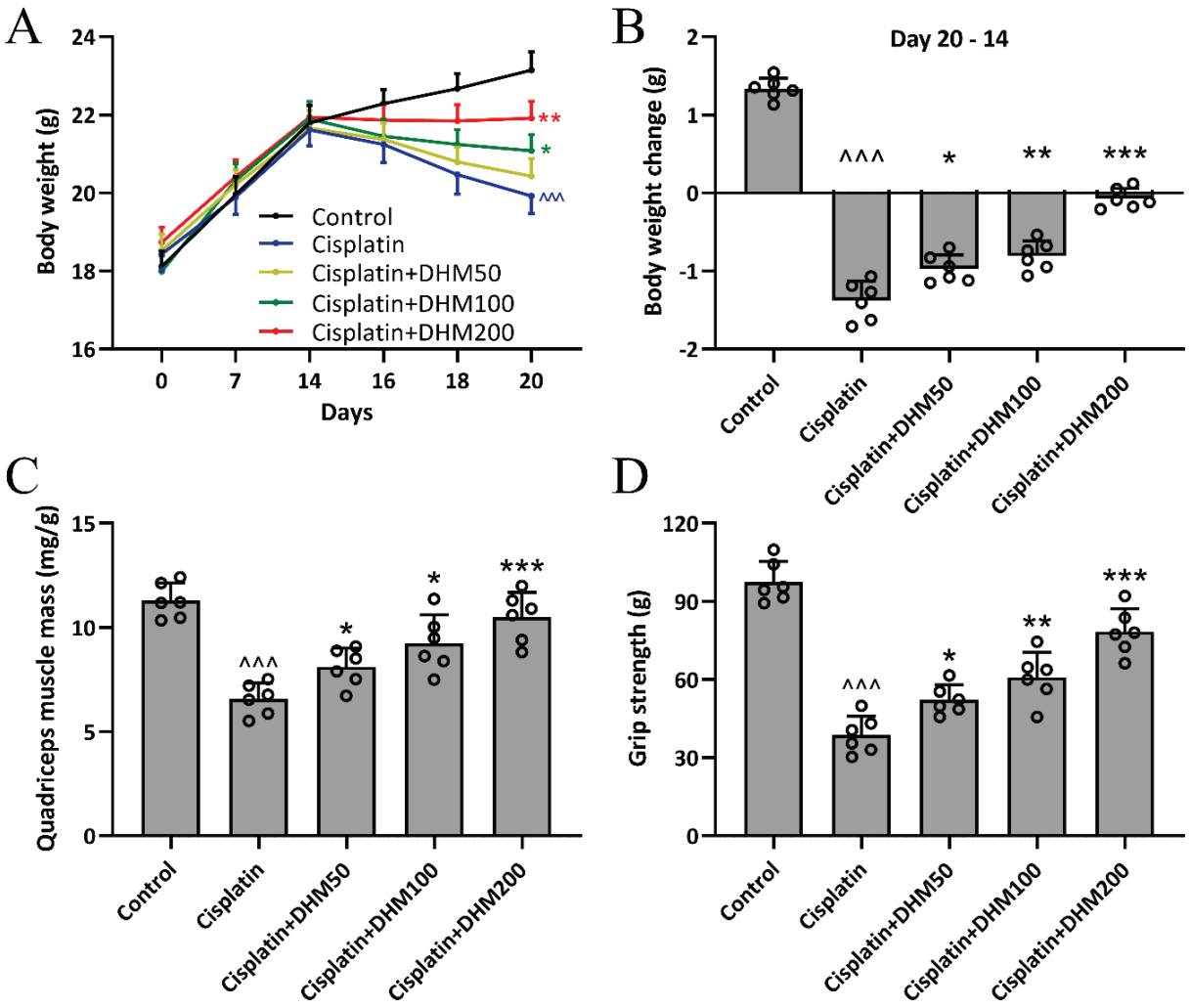
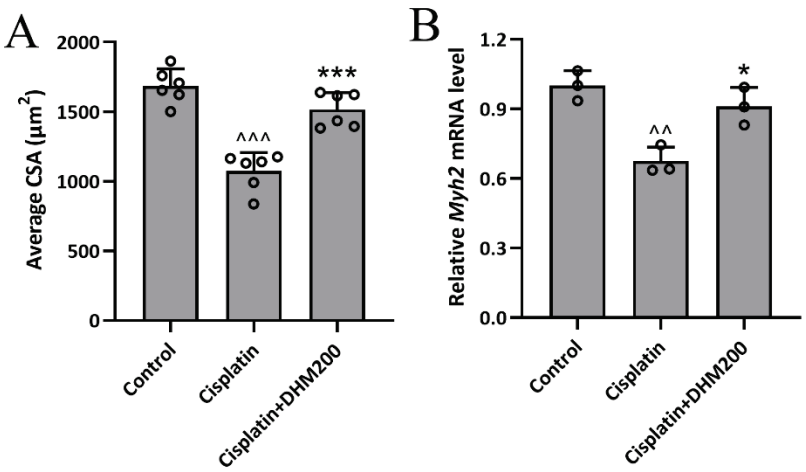


Fig. 1. The effects of Dihydromyricetin (DHM) on cisplatin-induced muscle atrophy *in vivo*. (**A**) Body weight change during the experiment. (**B**) Body weight change after cisplatin treatment for 6 days. (**C**) Quadriceps muscle mass was measured at day 20. (**D**) The grip strength was assessed using a grip strength meter. 6 mice were used for each group. Data were presented as mean ± SD. ^^^ $p<0.001$ compared to control. * $p<0.05$, ** $p<0.01$, *** $p<0.001$ compared to cisplatin group. One-way ANOVA followed Dunn's multiple comparisons test.



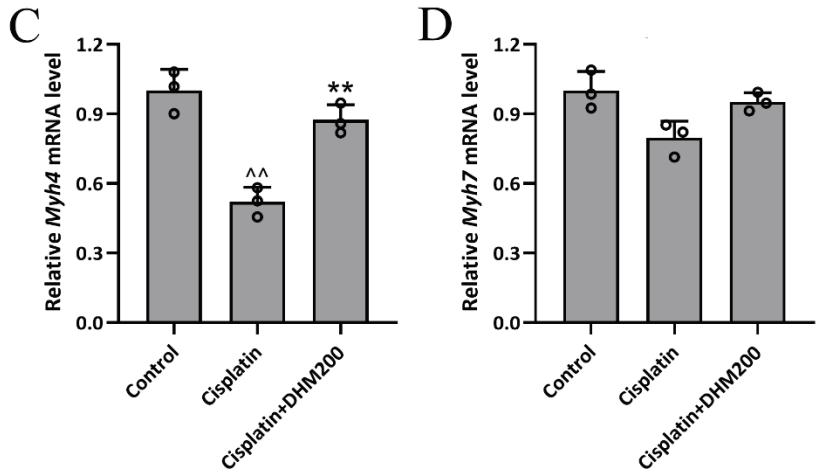
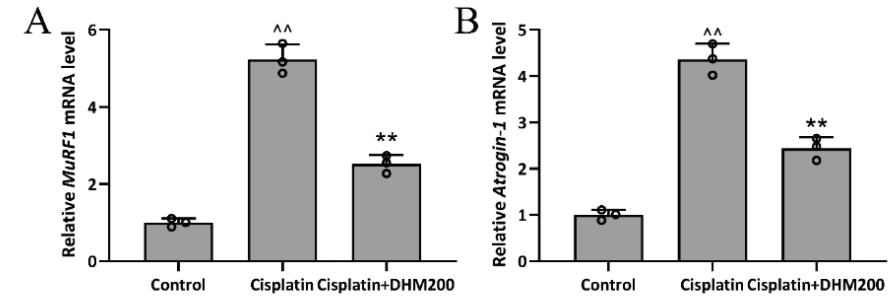


Fig. 2. The effects of Dihydromyricetin (DHM) on the cross-sectional area (CSA) of muscle fibers from mice after cisplatin treatment. (**A**) CSA in each group. 6 mice were used for each group. The mRNA levels of *Myh2* (**B**), *Myh4* (**C**), *Myh7* (**D**) in gastrocnemius muscles were tested by qRT-PCR. N=3 repeats for each group. Data were presented as mean ± SD. ^^ p<0.01, ^^^ p<0.001 compared to control. * p<0.05, ** p<0.01, *** p<0.001 compared to cisplatin group. One-way ANOVA followed Dunn's multiple comparisons test.



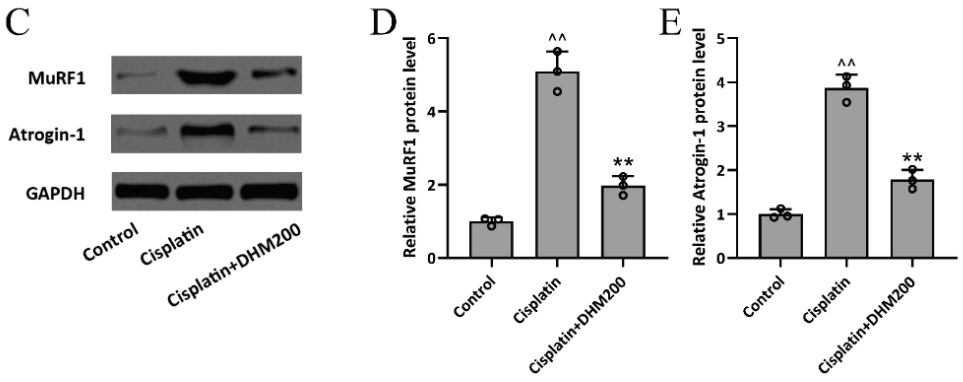


Fig. 3. The effects of Dihydromyricetin (DHM) on the expressions of MuRF1 and Atrogin-1 in muscles from mice after cisplatin treatment. The mRNA levels of *MuRF1* (**A**) and *Atrogin-1* (**B**) in gastrocnemius muscles were tested by qRT-PCR. (**C**) Western blotting was used to analyze the protein levels of MuRF1 and Atrogin-1 in gastrocnemius muscles. GAPDH was used as a loading control and the expressions were normalized to control (**D** and **E**). N=3 repeats for each group. Data were presented as mean ± SD. ^^ p<0.01 compared to control. ** p<0.01, compared to cisplatin group. One-way ANOVA followed Dunn's multiple comparisons test.

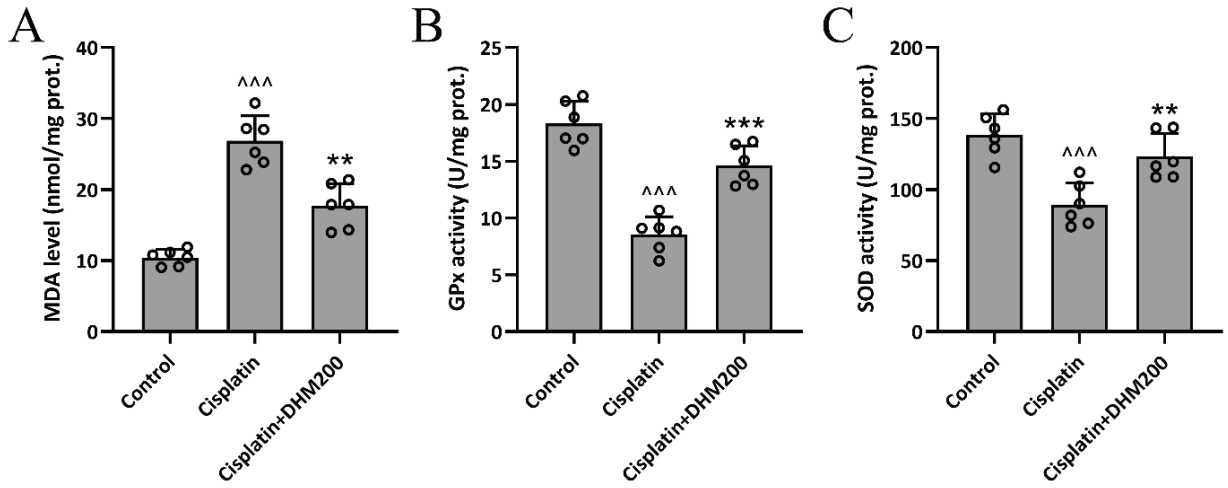


Fig. 4. The effects of Dihydromyricetin (DHM) on cisplatin-induced oxidative stress in mice. Levels of MDA (**A**), GPx activity (**B**) and SOD activity (**C**) in gastrocnemius muscles were measured. 6 mice were used for each group. Data were presented as mean ± SD. ^^^ $p<0.001$ compared to control. ** $p<0.01$, *** $p<0.001$ compared to cisplatin group. One-way ANOVA followed Dunn's multiple comparisons test.

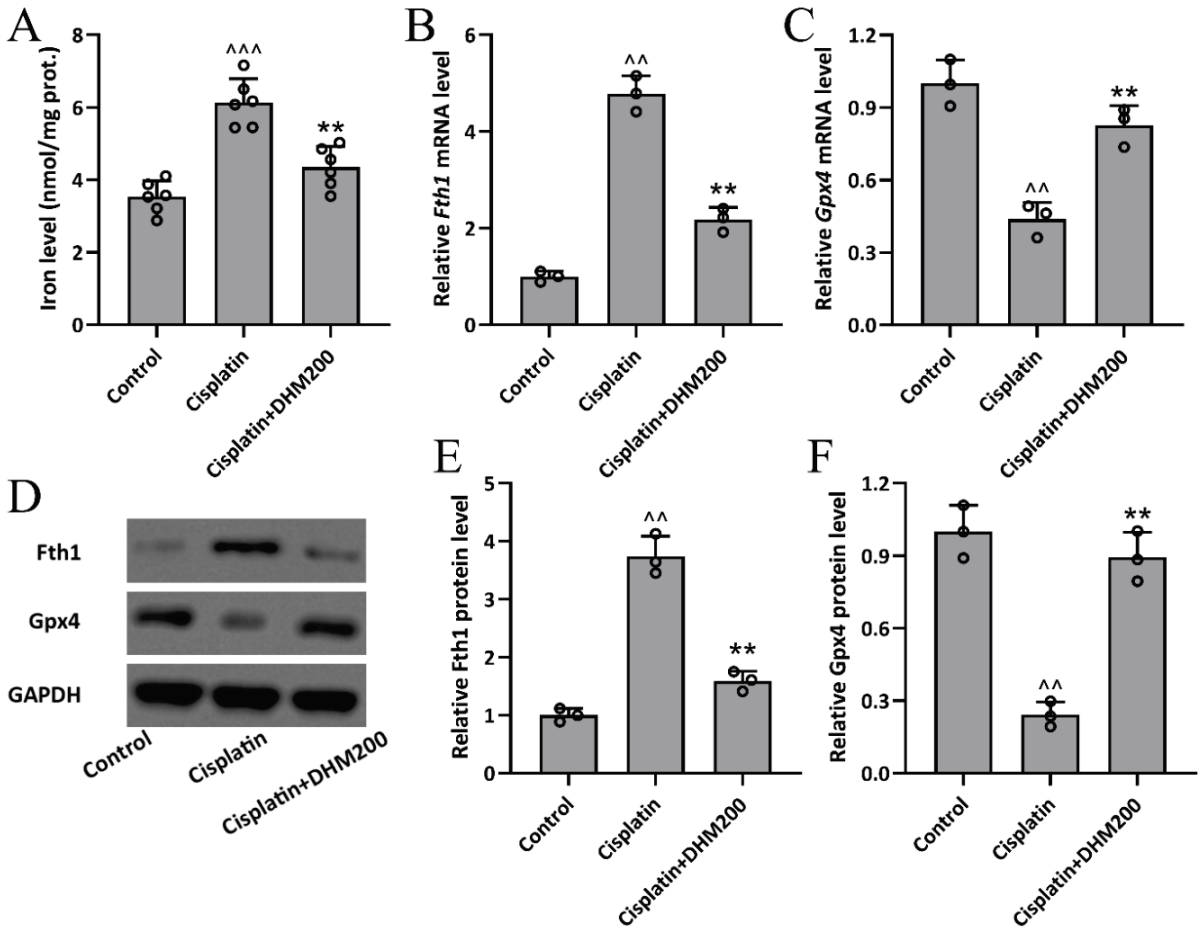


Fig. 5. The effects of Dihydromyricetin (DHM) on cisplatin-induced ferroptosis in mice. Levels of iron (**A**) in gastrocnemius muscles were measured. 6 mice were used for each group. The mRNA levels of *Fth1* (**B**) and *Gpx4* (**C**) in gastrocnemius muscles were tested by qRT-PCR. (**D**) Western blotting was used to analyze the protein levels of Fth1 and Gpx4 in gastrocnemius muscles. GAPDH was used as a loading control and the expressions were normalized to control (**E** and **F**). N=3 repeats for each group. Data were presented as mean ± SD. ^^ $p<0.01$, ^^^ $p<0.001$ compared to control. ** $p<0.01$, compared to cisplatin group. One-way ANOVA followed Dunn's multiple comparisons test.

It has been studied for its potential anti-inflammatory properties. Dihydromyricetin has been shown to suppress the production of pro-inflammatory cytokines, such as interleukin-1 beta, interleukin-6, and tumor necrosis factor-alpha [12]. Moreover, Dihydromyricetin could act as an inhibitor of the nuclear factor-kappa B signaling pathway [13]. Interestingly, it has been shown that Dihydromyricetin could inhibit ubiquitination. Ubiquitination is a process that marks proteins for degradation by the proteasome.

By targeting contractile and structural proteins, MuRF1 contributes to the breakdown of muscle fibers and the reduction of muscle mass. Inflammatory response, oxidative stress and ferroptosis in the setting of acute kidney injury could be induced by cisplatin [10]. Moreover, Hou *et al.* found that Dihydromyricetin reduced inflammation-triggered muscle atrophy by activating ryanodine receptor-CaMKK-AMPK signal pathway [8]. Therefore, we investigated whether Dihydromyricetin could attenuated cisplatin-induced muscle atrophy. In the present study, we found that Dihydromyricetin could effectively reduce cisplatin-induced muscle atrophy by inhibiting oxidative stress and ferroptosis that induced by cisplatin treatment.

Cisplatin treatment can lead to increased protein degradation in muscle cells, particularly through the activation of the ubiquitin-proteasome system, which is responsible for degrading misfolded proteins [14,15]. However, excessive activation of ubiquitin-proteasome in muscle cells can lead to muscle loss [14,15]. MuRF1 is an E3 ubiquitin ligase predominantly found in skeletal muscle [16,17].

It is upregulated during muscle atrophy in response to various triggers [18]. Atrogin-1 is another muscle-specific E3 ubiquitin ligase that is upregulated during muscle atrophy. In this study, we found that the protein levels of both MuRF1 and Atrogin-1 were significantly upregulated in Cisplatin-treated group, indicating an increase of muscle atrophy. Notably, treatment of Dihydromyricetin successfully reduced the levels of MuRF1 and Atrogin-1, thereby, attenuating muscle atrophy.

Moreover, Cisplatin can induce oxidative stress in muscle tissues. Increased production of reactive oxygen species results in damaging muscle cells and muscle atrophy [19,20]. Study has shown Dihydromyricetin exhibits antioxidant properties by neutralizing free radicals and protects cells from damage and reduces inflammation [21,22]. Consistent with previous studies, we found that Dihydromyricetin treatment significantly reduced peroxidative product MDA level to that of control. Moreover, antioxidants GPx and SOD activities were restored in the Dihydromyricetin group back to almost control. Oxidative stress induced by cisplatin was reduced by Dihydromyricetin treatment.

Ferroptosis is a process of regulation of cell death *via* iron-dependent lipid peroxidation, which results in the accumulation of reactive oxygen species and damage to cell membranes. Fth1 is involved in storing and releasing iron in a controlled manner to maintain cellular iron homeostasis [23]. Gpx4 can protect cells from lipid peroxidation [24]. Cisplatin treatment arise ferroptosis characterized by increase of Fth1 and reduction of Gpx4 [25-27], contributing to patient muscle atrophy. Wu *et al.* have shown that targeting ferroptosis induced by cisplatin successfully reduced oxidative stress and muscle loss caused by cisplatin [28]. Moreover, Xie *et al.* demonstrated that Dihydromyricetin can alleviate cerebral ischemia reperfusion injury by inhibiting ferroptosis [29]. In this study, our data showed that Dihydromyricetin reduced iron level in gastrocnemius muscle. In parallel, mRNA and protein levels of Fth1 were repressed and Gpx4 were restored by Dihydromyricetin treatment. Overall, these findings indicated that Dihydromyricetin can protect gastrocnemius muscles from cisplatin-induced ferroptosis.

There are some limitations in the presented study. First, 5-week-old male mice were used in this study. To avoid age and gender bias, older mice and female mice should be included for the further study. Second, Dihydromyricetin were pretreated for 14 days before cisplatin, which might be difficult to pretreat patients with Dihydromyricetin before giving cisplatin. To better mimic clinical setting, we will administrate mice with Dihydromyricetin and cisplatin at the same time. In addition, it has been demonstrated that Dihydromyricetin has a strong effect on muscle atrophy induced by cisplatin, it would be interesting to examine whether the anti-cancer activities and efficacy are changed or not under Dihydromyricetin treatment.

Conclusions

The present study demonstrated that Dihydromyricetin acts as an effective pharmacological agent in attenuating cisplatin-induced muscle atrophy by reducing skeletal muscle E3 ubiquitin-protein ligases, oxidative stress, and ferroptosis.

Conflict of Interest

There is no conflict of interest.

Acknowledgements

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Abbreviations

AMPK, Adenosine 5'-monophosphate (AMP)-activated protein kinase; ANOVA, analysis of variance; Atrogin-1, muscle atrophy F-box; CaMKK, calmodulin-dependent protein kinase kinase; DHM, Dihydromyricetin; Fth1, ferritin heavy chain 1; GAPDH, glyceraldehyde-3-phosphate dehydrogenase; GPx, glutathione peroxidase; MDA, malondialdehyde; MuRF1, muscle RING-finger protein 1); Myh, myosin heavy chain; qRT-PCR, quantitative real-time polymerase chain reaction; SD, standard deviation; SOD, superoxide dismutase

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