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Herniarin Alleviates Sodium Arsenite-Induced Liver Toxicity in Mice by Attenuation of Oxidative Stress and Inflammation

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Abstract

Background: Arsenic is a serious threat to human health. Long-term exposure to arsenic has been linked to various harmful health effects, including liver damage. The liver damage caused by arsenic is mainly due to inflammation and oxidative stress. This research was performed to investigate the hepatoprotective effects of herniarin (HER), a coumarin derivative found in many plants, against hepatotoxicity induced by sodium arsenite (SA).

Methods: To induce hepatotoxicity, SA at a dose of 10 mg/kg was administered to mice for 30 days. HER at doses of 10, 25, and 50 mg/kg was given to mice for 30 days before SA administration. After completing the study protocol, the animals were euthanized, and blood and liver samples were collected for biochemical assessments.

Results: The results showed that SA increased liver enzymes and causes tissue damage, as well as elevated oxidative substances such as substances reactive to thiobarbituric acid in the liver, while simultaneously leading to a decrease in total thiol reserves and decreases in antioxidant enzymes such as catalase, superoxide dismutase, and glutathione peroxidase. Western blot analysis showed decreased protein expression of Nrf2, NQO1, and HO-1.

Conclusions: Pretreatment with HER ameliorated SA-associated liver injury in mice. HER reduced hepatotoxicity and oxidative damage caused by SA and increased antioxidant factors.

Keywords: Arsenic, Hepatotoxicity, Herniarin, Nrf2, Oxidative stress.

Introduction

Arsenic is a toxic metalloid that exists in the environment due to natural processes or human activities. This substance can enter the human body through ingestion or inhalation, and once inside the body, it is absorbed by the digestive system and lungs, enters the bloodstream, and spreads throughout other organs (1, 2). The World Health Organization (WHO) set the maximum permissible limit for arsenic in drinking water at 50 micrograms per liter and the safe limit at 10 micrograms per liter (3). The correlation between exposure to arsenic and liver disorders such as hepatomegaly and hepatocellular carcinoma has been observed in various studies, indicating that liver is a major target organ for arsenic toxicity (4). Arsenic disrupts biological systems by generating excess reactive oxygen species (ROS) and inhibiting oxidation-reduction reactions (Redox) (5). Studies suggest that arsenic

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inhibits enzymes involved in fatty acid synthesis, glucose absorption, and glutathione oxidation and synthesis by binding to sulfhydryl groups (6).

Herniarin (HER) or 7-methoxycoumarin is a coumarin derivative that is naturally found in flowering plants. It is one of the most abundant coumarin derivatives and has several pharmacological properties, such as anti-inflammatory, inhibitory, antioxidant, and analgesic properties. Additionally, it has been reported to have anticytotoxic effects in some cell lines, including MCF7 and laryngeal cancer cell lines (7, 8).

Nuclear factor erythroid 2-related factor 2 (Nrf2) is a transcription factor that regulates the expression of various genes involved in antioxidant defense and detoxification pathways. When Nrf2 is activated by oxidative stress or exposure to toxins like arsenic, it translocates moves to the nucleus of cells and attaches to specific DNA sequences known as antioxidant response elements (AREs). This process leads to the activation of genes that produce antioxidant enzymes and phase II detoxification enzymes, such as NQO1(NAD(P)H: quinone oxidoreductase 1) and heme oxygenase-1 (HO-1) (9). HO-1 is an enzyme that breaks down heme into biliverdin, carbon monoxide, and iron. This process helps to reduce oxidative stress and inflammation (10). NQO1 reduces and removes quinones and other electrophilic compounds, thereby playing a crucial role in detoxification processes. It also acts as an antioxidant by regenerating other antioxidants such as vitamin E (11).

Additionally, arsenic-induced inflammation further exacerbates liver injury through the activation of pro-inflammatory signaling pathways. On the other hand, nuclear factor kappa B (NF-κB) is a transcription factor that plays an important role in regulating genes involved in immune and inflammatory responses (12, 13).

This study aimed to investigate the protective effects of HER on the liver against hepatotoxicity caused by sodium arsenite through reducing oxidative stress and inflammation in mice.

Materials and Methods

Animals

Forty-two male NMRI mice, weighing between 27-35 grams and aged 6-8 weeks, were acquired from the Experimental Animal house of Jundishapur University of Medical Sciences, Ahvaz. The animals were kept in standard cages under optimal conditions at room temperature, with a relative humidity of 45-55%, and a 12-hour light-to-dark cycle. They were fed a standard diet and had access to clean drinking water ad libitium. The study was conducted by the code of ethics for animal experiments (IR.AJUMS.ABHC.REC.1401.067) and was approved by the Animal Ethics committee of Ahvaz Jundishapur University of Medical Sciences.

Experimental design and treatment protocol

Mice were allocated to six groups (n=7). The first control group received distilled water orally for 30 days, the HER-treated group received herniarin (HER, 50 mg/kg; Gol Elixir Pars Company, CAS No: 531-59-9) by gavage for 30 days. The third group received sodium arsenite (SA, 10 mg/kg; Sigma-Aldrich, USA) by gavage for 30 consecutive days. The fourth, fifth, and sixth groups received **SA** + HER at doses of 50, 25, and 10 mg/kg, respectively. In groups 4, 5, and 6, SA was administered one hour after HER treatment. Twenty-four hours after the last administration (day 31), the mice were anesthetized by intraperitoneal injection of ketamine (100 mg/kg) and xylazine (10 mg/kg). Blood samples were collected from the hearts of the mice, centrifuged at a speed of 500 G for 15 min., and the serum were collected for liver tests. The liver tissue was kept in a -70 °C to evaluate oxidative stress and protein expression biomarkers.

Serum biochemistry

AST, ALT, and ALP levels were determined using the commercial kit protocols (Pars Azmoon, Tehran, Iran).

Measurement of oxidative stress indicators in liver tissues

To determine the protein concentration in the supernatants of homogenized liver tissue, the Bradford method was used. An animal's liver was divided into equal parts and homogenized assay buffer (RIPA) containing protease inhibitors (14). The homogenates were then centrifuged (4000 ×g for 20 min at 4 °C).The amount of glutathione peroxidase (GPX) enzyme activity and SOD (ZB-SOD-96A) of the tissues was measured according to the ZellBio commercial kit (ZB-GPX-A48, Germany) by the Paglia and Valentine method (15).

The total thiol content was determined using the Ellman reaction and DTNB (5,5-dithio-bis-(2-nitrobenzoic acid) (Sigma-Aldrich Co., USA) reagent. To perform the test, the supernatant was mixed with Ellman's reagent (0.01 M) and incubates at room temperature for 20 minutes. After the incubation period, the yellowish solution was analyzed for absorbance at 412 nm using a microplate reader (16).

The catalase activity was measured by the Shangari method (17). To prepare the sample, 10 µL of the homogenized solution was added to a mixture of 50 µL of phosphate buffer and 100 µL of H2O2. The mixture s was incubated at room temperature for 10 minutes. During this time, the catalase enzyme will convert H2O2 into water and oxygen molecules while the remaining H2O2 in the sample reacts with ammonium molybdate (Merck Co., Germany). Then, 10 µL of ammonium molybdate was added to the mixture, the absorbance as IU/mg protein at a wavelength of 410 nm using a microplate reader.

Lipid peroxidation assay (TBARS)

To assess lipid peroxidation, thiobarbituric acid reagents (TBARS) were measured. The supernatant was mixed with 30% trichloroacetic acid solution in phosphate buffer and centrifuged at 3500 x g for 15 minutes. Then the supernatant was transferred to microtubes, mixed with TBA reagent and incubated in a warm water bath. The absorbance of the resulting pink color was measured at a wavelength of 532 nm (18).

Western blot analysis of Nrf2, NQO1, HO-1 and NF-κB

To conduct the Western blot test, we used tissue samples that had been frozen in a -70 °C freezer. These samples were homogenized to prepare tissue homogenates. To separate the samples, we used SDS-PAGE gel (12%) and transferred them onto polyvinylidene fluoride (PVDF) gel membranes. We incubated the samples first with the primary antibody at 4 °C and then with the secondary antibody (mouse anti-rabbit IgG-HRP: sc-2357; Santa Cruz, CA, USA). The primary antibodies used, and their respective dilutions were Nrf2 (1:1000), NQO1 (1:1000), HO-1 (1:1000), GAPDH (1:1000), and NF-κB (1:1000).

Statistical analysis

GraphPad Prism version 9.0.0 was used for statistical analysis. One-way analysis of variance (ANOVA) followed by Tukey's post hoc test was performed to determine significant differences between groups. The significance level was considered as $p<0.05$.

Results

Effects of HER on serum markers of liver function

To investigate the effect of HER on liver damage caused by SA, serum concentrations of AST, ALT, and, ALP enzymes were tested. In the SA group, the level of these markers increased significantly ($p<0.001$) compared to the control group (Fig. 1). Administration of HER one hour after arsenic, with doses of 50 and 25 mg/kg, significantly improved the increase of AST (Fig.1A), ALT (Fig. 1B), and ALP (Fig. 1C) in serum in mice exposed to arsenic.

Effect of HER on liver oxidative stress markers

In the group exposed to SA, a statistically significant increase in TBARS level was observed (Fig. 2A), and the levels of antioxidant markers, including total thiol, CAT, SOD, and GPx (Figs. 2B, 2C, 2D, and 2E), significantly decreased in comparison to the control group. HER-pretreated groups at doses of 25 and 50 mg/kg improved the levels of liver TBARS, and the enzymatic activities

of SOD, CAT, and GPx. Also, pretreatment with HER at a dose of 50 mg/kg, restored the reduced level of total thiol in SA-exposed mice. In the group exposed to SA, a significant increase in the level of TBARS (Fig.2A), along with a significant decrease in the levels of antioxidant markers, was observed. They comprise total thiol, CAT, SOD, and GPx in comparison to the control group (Figs. 2B, C, D, and E). However, liver TBARS levels improved and SOD, CAT, and GPx enzyme activity increased in groups pretreated with HER at dosages of 25 and 50 mg/kg. Additionally, pretreatment with HER at a dose of 50 mg/kg restored the reduced level of total thiol in SA-exposed mice.

Effect of HER on the liver expression of Nrf2, HO-1, NQO1, and NF-κB proteins

A statistically significant decrease in protein expression Nrf2, HO-1, and NQO1 (Fig.3 A, B, C) and an increase in the protein expression of NF-κB (Fig. 3) were observed in SA-exposed mice compared with the control group. Treatment with HER at doses of 25 and 50 mg/kg significantly decreased NF-κB protein expression compared to the SA group and significantly increased the expression of Nrf2, HO-1, and NQO1 proteins compared to the SA group ($p< 0.01$). When comparing SA-exposed animals to the control group, a significant decrease in the protein expression of Nrf2, HO-1, and NQO1 (Figs. 3A, 3B, and 3C) and an increase in the protein expression of NF-κB (Fig. 3D) were observed. HER treatment at doses of 25 and 50 mg/kg considerably enhanced the expression of Nrf2, HO-1, and NQO1 proteins ($p< 0.01$) and significantly decreased the expression of NF-κB protein compared to the SA group.

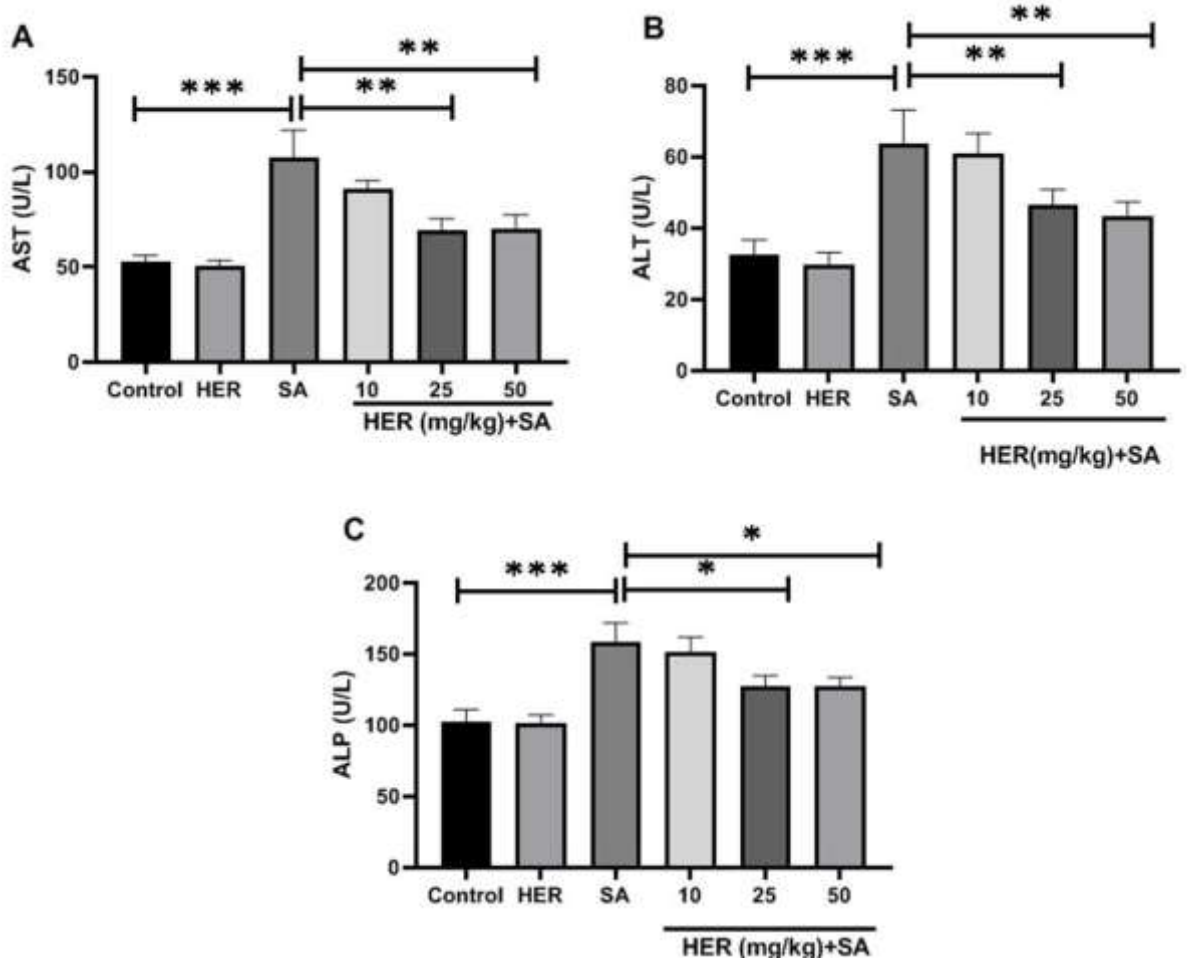

Fig. 1. Effect of herniarin on serum markers of liver function in sodium arsenite-induced hepatotoxicity. (A) AST, (B) ALT, and (C) ALP. All values are expressed as mean ± SD of 7 animals/group.
(*P< 0.05, **P< 0.01, ***P< 0.001).

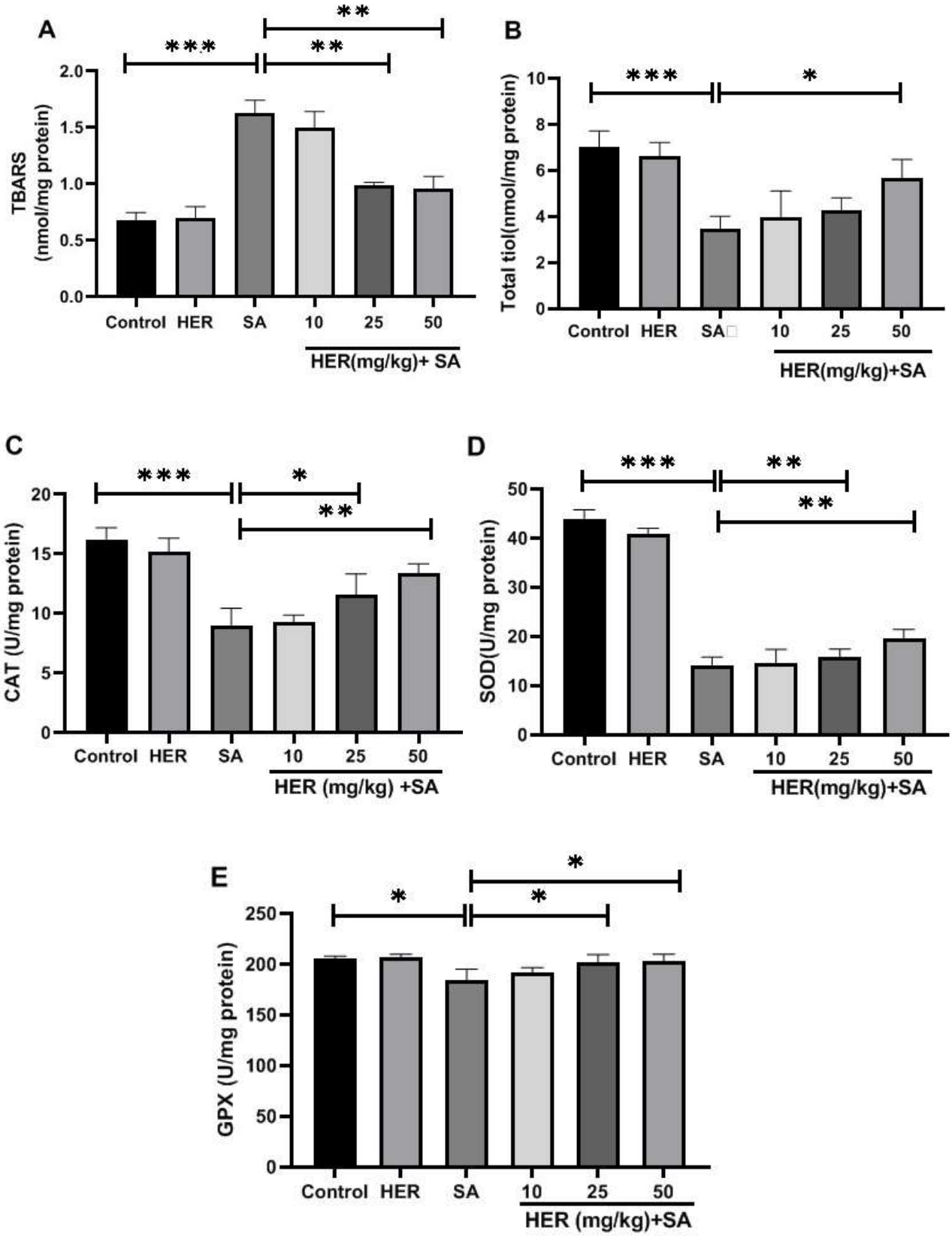

Fig. 2. Effect of herniarin on oxidative stress markers in liver of mice with sodium arsenite-induced hepatotoxicity.(A) Thiobarbituric acid reactive substances (TBARS), (B) Total thiol, (C) Catalase (CAT), (D) Superoxide dismutase (SOD), and (E) Glutathione peroxidase (GPx). All values are expressed as mean ± SD of 7 animals/group. (*P< 0.05, **P< 0.01, ***P< 0.001).

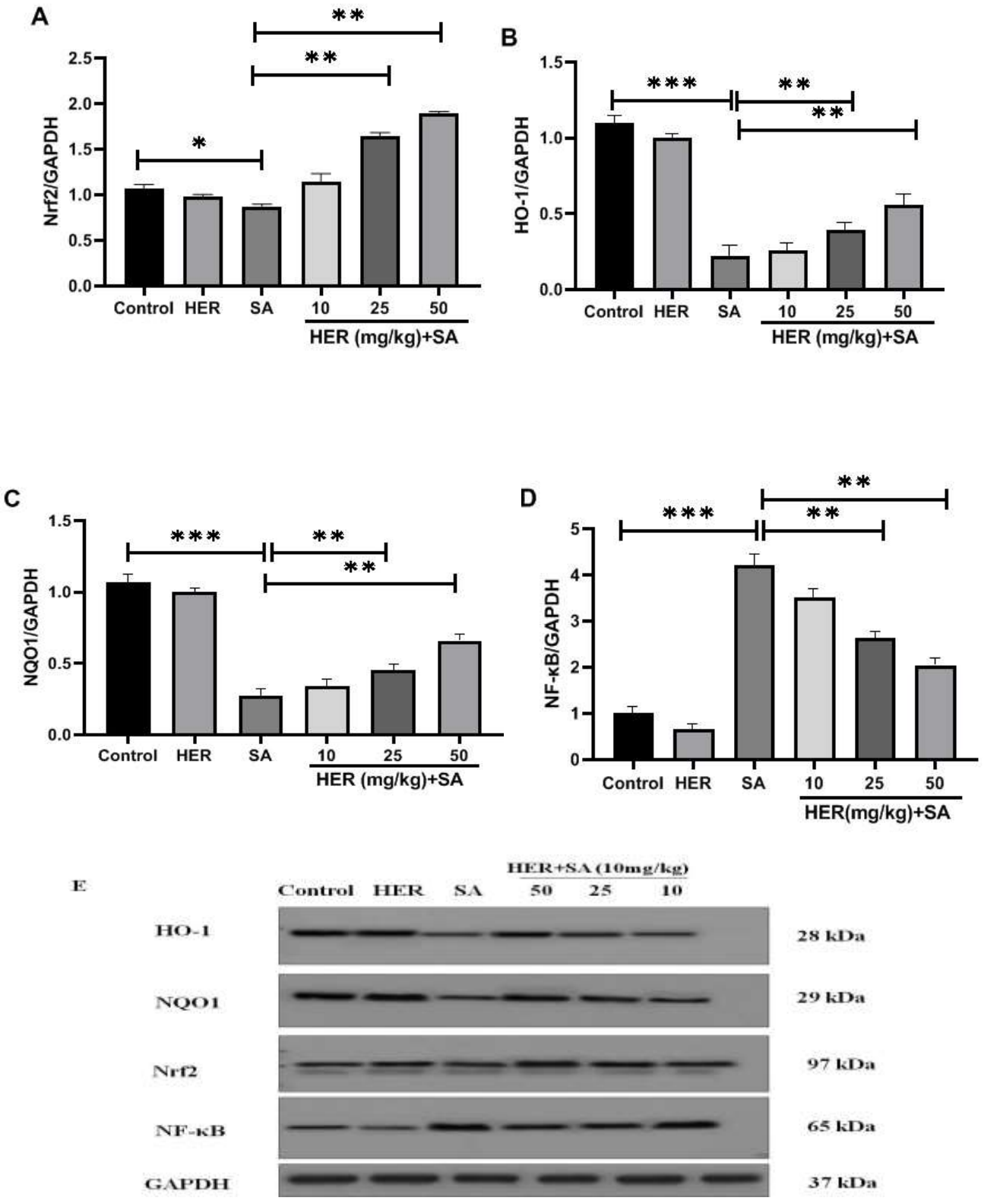

Fig. 3. Effect of herniarin on expression of (A) Nrf2, (B) HO-1, (C) NQO1 and (D) NF-κB in the liver of mice with sodium arsenite-induced hepatotoxicity. (E) Western blot analysis of liver tissue in the studied groups. (*P< 0.05, **P< 0.01, ***P< 0.001)

Discussion

Arsenic exposure leads to oxidative stress and liver damage by reducing antioxidant systems, increasing intracellular ROS, and altering antioxidant defences (19, 20). Several enzymes, including superoxide dismutase (SOD), catalase (CAT), and glutathione peroxidase (GPX), as well as non-enzymatic compounds such as tocopherol, vitamin E, beta-carotene, ascorbate, and total thiols, carry out protective actions against ROS (21). Nuclear factor erythroid 2 (Nrf2) has a crucial function in defending tissues against high levels of oxidative species and toxic damage. When the body undergoes oxidative stress, Nrf2 enters the nucleus and begins transcribing target genes. This process activates enzymes responsible for detoxification, as well as antioxidant proteins such as Hmox-1 and NQO1. Several studies have shown that activating the Nrf2 pathway can improve various liver disorders (22). Studies indicate that plant polyphenols can enhance the expression of HO-1 and SOD via the Nrf2/ARE pathway. Polyphenolic compounds induce conformational changes in cytoplasmic Nrf2, leading to its translocation to the nucleus (23). HER is a derivative of coumarin, which is known to have numerous biological activities, such as antibacterial, antifungal, anti-clotting, anti-inflammatory, and antioxidant properties (24). The study by Bose et al. revealed that HER reduces breast cancer progression in Sprague-Dawley rats by altering metabolic pathways (8).

Studies have shown that exposure to arsenic can cause a significant increase in serum levels of ALT, AST, and ALP, which are markers of liver damage. Additionally, arsenic exposure has been found to increase ALP activity in the plasma and liver of cancer patients. Collectively, the results from these studies demonstrate that arsenic has the potential to compromise both the structural and functional integrity of the liver (25). Our study findings indicated that exposure to arsenic results in significant liver damage, as confirmed by increased serum levels of ALP, AST, and ALT. Furthermore, histopathological analysis revealed liver tissue damage in the arsenic group, which is consistent with the findings of previous studies (24). In our study, we observed that the administration of HER at doses of 50 and 40 mg/kg effectively decreased the elevation in AST, ALT, and ALP levels, as well as mitigated liver damage caused by SA-induced TBARS. TBARS are a collection of small lipid peroxidation byproducts, predominantly malondialdehyde, which is one of the end products of lipid peroxidation. The measurement of TBARS is commonly employed to evaluate lipid peroxidation resulting from oxidative stress (26). Studies have found a direct correlation between the level of arsenic in blood and urine samples and the level of lipid peroxidation. TBARS can be used as an index to measure oxidative stress in plasma and urine (27). The results of several studies showed that HER has antioxidant properties and increases the level of CAT, SOD, total thiols, and GPX and decreases the level of TBARS (28, 29). During this study, it was observed that the amount of lipid peroxidation in mice treated with HER decreased, while levels of antioxidant indices increased. In this study, the effect of HER on the activation of Nrf2 pathway to reduce arsenic-induced hepatotoxicity was investigated. The results showed increased Nrf2 activity and the increased expression of NQO1 and HO-1 proteins in mice treated with HER.

Nuclear factor κB (NF-κB) is a transcription factor that activates the expression of genes involved in inflammatory, immune, and acute phase responses (30). The results of a study showed that arsenic increases the expression of nuclear factor kappaB (NF-κB) in mouse liver tissue (31).Our study showed that HER reduced NF-κB activity and, thus, SA-induced inflammation in arsenic-exposed rats. Finally, according to the results, SA-induced increases in ROS cause inflammation and oxidative stress in liver cells. HER activates the Nrf2 signaling

pathway and increases the expression of HO-1 and NQO1.

Herniarin treatment can alleviate SA-induced liver injury in mice. This study showed that the hepatoprotective effects of HER, particularly at doses of 25 and 50 mg/kg, are mediated through the regulation of oxidative stress and inflammation. HER inhibited SA-induced hepatotoxicity by down- regulating the expression of NF- κB protein and increasing the expression of Nrf2, HO-1, and NQO1 proteins (Fig. 4). Additionally, HER attenuated SA-induced liver injury by enhancing antioxidant defences. Therefore, individuals exposed to SA levels exceeding WHO guidelines may benefit from HER supplementation. However, further studies are needed to elucidate the protective mechanisms of HER and its effectiveness in humans.

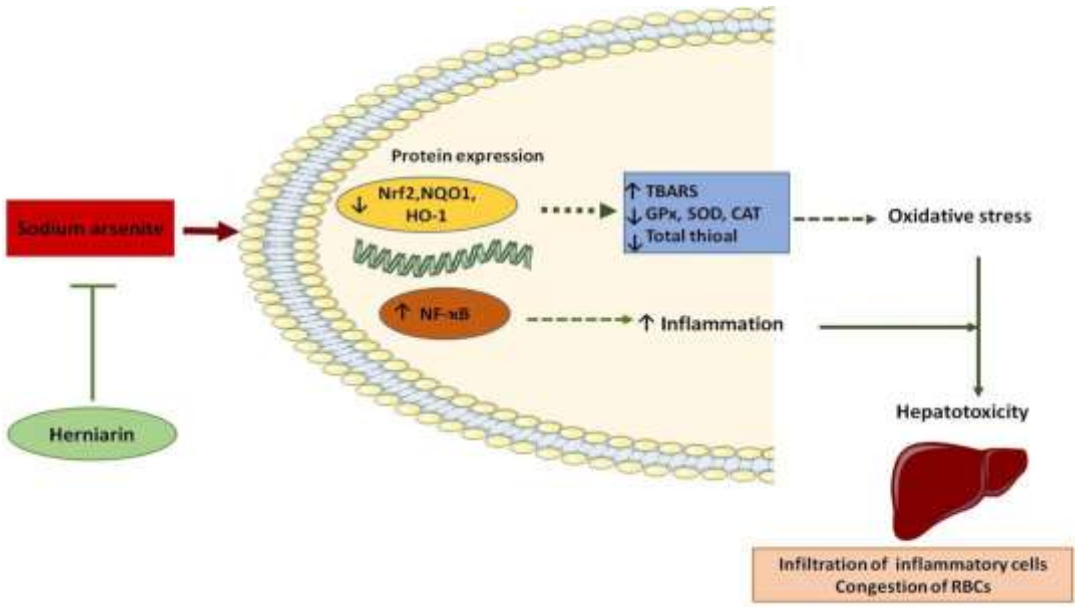

Fig. 4. The schematic of the hepatoprotective effects of herniarin on sodium arsenite-induced liver toxicity in mice.

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Competing Interest

There are no conflicts of interest to declare.

Ethics Approval

The study was approved by the Ethics Committee of the Ahvaz Jundishapur University of Medical Sciences (IR.AJUMS.ABHC.REC.1401.067).

Authors contribution

Faride Alvandi: Methodology, Investigation, Resources, Writing – original draft, Visualization. Mehrnoush Matin: Writing – review, Software, Data curation. Maryam Salehcheh: Conceptualization, Supervision, Writing – review & editing. Layasadat Khorsandi: Formal analysis, Data curation. Mehrnoosh Moosavi: Conceptualization, Methodology, Validation, Writing – review & editing, Project administration.

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