Original Research Article | J Adv Med Biomed Res. 2025; 33(160): 156-166

Category: Pharmacology | Peer Reviewed | Open Access

Journal of Advances in Medical and Biomedical Research | ISSN:2676-6264

Protective Effects of *Sanguisorba minor* and Chlorogenic Acid Against Doxorubicin-Induced Cardiotoxicity in Rats

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Article Info

10.30699/jambr.33.160.156

Received: 2025/05/15;
Accepted: 2025/11/01;
Published Online: 11 Nov 2025;

Use your device to scan and read the article online

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ABSTRACT

Background & Objective: Doxorubicin (Dox) is used in chemotherapy, but its usage is restricted due to cardiotoxicity. *Sanguisorba minor* (*S. minor*) and chlorogenic acid (CGA) exhibit pharmacological activities, including the reduction of oxidative stress and induction of programmed cell death. In this investigation, the cardioprotective effects of *S. minor* and CGA were evaluated following Dox-stimulated toxicity in rats.

Materials & Methods: Forty male Wistar rats were used in this research. Saline was administered to the control group; Dox (2.5 mg/kg, intraperitoneally, on alternate days) was injected to the toxicity group; In the second week, groups III and IV received oral *S. minor* extract at 100 or 300 mg/kg; and Group V received CGA (40 mg/kg, intraperitoneally). Serum levels of lactate dehydrogenase (LDH) and creatine kinase-MB (CK-MB) were quantified as cardiac injury markers. Cardiac tissues were analyzed for superoxide dismutase (SOD) activity, malondialdehyde (MDA) levels, and thiol content. The modification of histopathology was studied via hematoxylin and eosin (H&E) staining.

Results: Dox increased LDH, CK-MB, and MDA levels and reduced SOD and thiols. The administration of *S. minor* and CGA ameliorated Dox-induced biochemical changes. Histopathological analysis demonstrated extracellular edema, moderate congestion, and localized hemorrhage following Dox exposure. These effects were mitigated by treatment with *S. minor* and CGA.

Conclusion: The administration of *S. minor* and CGA provided significant protection against Dox-related cardiotoxicity, likely through the modulation of oxidative stress pathways and preservation of myocardial structure.

Keywords: Doxorubicin, Chlorogenic Acid, *Sanguisorba minor*, Cardiotoxicity, Oxidative Stress, Antioxidant Agent

1. Introduction

Doxorubicin (Dox) is an anthracycline drug applied for the treatment of different types of cancer (1). Clinical evidence has shown that cumulative doses of Dox can lead to significant cardiac damage in patients, thereby limiting its long-term use (2). Few drugs are available for protection against Dox-stimulated cardiotoxicity. One of these agents, which is approved by the FDA as a cardioprotective compound following Dox consumption, is dexrazoxane (3).

However, the use of dexrazoxane is limited due to several issues, such as the attenuation of the chemotherapeutic effect of Dox in patients (4, 5). Thus, it is necessary to identify therapeutic compounds that reduce the cardiotoxicity of Dox without affecting its anti-cancer activity. Various factors contribute to the toxicity of Dox, among which the elevation of reactive oxygen species (ROS) has a prominent role, whereas mitochondrial injury, the dysregulation of calcium hemostasis, autophagy, and inflammation have less significant effects (6). Moreover, the reduction of some factors, such as

erythroid-derived 2-like 2 (Nrf2)/heme oxygenase-1 (HO-1), has been reported in the cardiac toxicity of Dox (7).

Therefore, researchers are attempting to identify compounds with cardioprotective effects that exhibit fewer side effects. Studies have reported that many phytochemicals exert protective effects as prophylactic agents by reducing xenobiotic-stimulated DNA damage, apoptosis, inflammation, and oxidative stress (8).

Sanguisorba minor (*S. minor*) is a member of the Rosaceae family, which was used for the treatment of diarrhea, eczema, and bleeding in the past (9). The pharmacological properties of *S. minor* include neuroprotective, anti-cancer, antibacterial, and anti-inflammatory effects (9-11). The presence of various compounds, such as terpenoids, flavonoids, phenols, and especially polyphenolic acids, is responsible for its diverse pharmacological properties (9). Chlorogenic acid (3,4-dihydroxycinnamate, CGA), as a polyphenolic, is identified in many plants, such as *Vaccinium angustifolium, Crataegus monogyna*, and *S. minor* (12, 13). Numerous investigations have indicated that CGA has various therapeutic effects, including anti-diabetic, anti-obesity, cardioprotective, neuroprotective, anti-tumor, hepatoprotective, and analgesic properties (14). According to the literature, CGA reduced myocardial infarction via the upregulation of Nrf2/HO, thereby stabilizing mitochondrial and lysosomal enzymes (15-17). While numerous antioxidants have been investigated for their cardioprotective effects, *S. minor* and CGA were selected due to their accessibility, rich polyphenolic composition, and previously demonstrated in vivo cardiovascular benefits. The present research aimed to explore the cardioprotective potential of *S. minor* and CGA following Dox-induced myocardium toxicity. In this research, the levels of cardiac enzymes and oxidative stress parameters were evaluated.

2. Materials and Methods

2.1 Reagents

Dox, ketamine/xylazine anesthetic compounds, and 2-thiobarbituric acid (TBA) were obtained from Sigma-Aldrich (St. Louis, MO, USA). Pyrogallol and 2, 2′-dinitro-5, 5′-dithiodibenzoic acid (DTNB) were procured from Cayman Chemical (Michigan, USA). CGA was provided by the Golexir Company.

2.2 The extraction of *S. minor*

The aerial parts of *S. minor* were obtained from Ghoochan, Khorasan Razavi Province, Iran, and taxonomically authenticated by M.R. Joharchi at Ferdowsi University of Mashhad (voucher no. 45489). The plant material was dried, pulverized, and extracted with 400 mL of 70% ethanol for 48 h. The filtrate was then concentrated under reduced pressure at 37°C using a rotary evaporator.

2.3 Animals

Adult male Wistar rats (200–250 g) were housed in the Animal Research Center of Mashhad University of Medical Sciences under controlled conditions (22 ± 4°C, 12-h light/dark cycle) with free access to standard chow and water. All procedures adhered to the NIH Guide for the Care and Use of Laboratory Animals and were approved by the Ethics Committee of Mashhad University of Medical Sciences (approval code: IR.MUMS.MEDICAL.REC.1400.715).

2.4 Animal groups

In this research, 40 rats were used and divided into five groups of eight. Group I (control): received intraperitoneal injections of 0.9% saline; Group II: received Dox intraperitoneally at a dose of 2.5 mg/kg on alternate days for 14 days (cumulative dose: 15 mg/kg) (18); Groups III and IV: received oral *S. minor* at doses of 100 and 300 mg/kg one week after the beginning of Dox treatment; and Group V: CGA was administered via oral gavage at a dose of 40 mg/kg in the second week. The *S. minor* extract doses were chosen according to our previously published studies (19, 20), in which the *S. minor* extract did not significantly affect cardiac and hepatic functions or morphology. The CGA dose was selected based on earlier literature using the isoproterenol-induced myocardial injury model (17).

2.5 Sample collection

The anesthetization of rats was conducted by ketamine (90 mg/kg) and xylazine (10 mg/kg) on the 15th day. Then, 5 mL of blood was collected from the heart, and serum was separated via centrifugation. The sera were incubated at -20°C to measure lactate dehydrogenase (LDH), as well as muscle and brain creatinine kinase (CK-MB). Moreover, cardiac samples were collected for pathological and biochemical studies. Finally, 10% homogenized cardiac tissue samples were prepared using cold KCl solution (1.5%, pH = 7) to evaluate superoxide dismutase (SOD) activity, malondialdehyde (MDA) levels, and thiol levels.

2.6 The evaluation of cardiac enzymes

The levels of LDH (Man Company, Iran) and CK-MB (Biorexfars, Iran) in the serum samples were measured using standard kits according to the manufacturers' instructions. CK-MB was measured using a UV-optimized test according to International Federation of Clinical Chemistry and Laboratory Medicine (IFCC) guidelines, and LDH activity was determined based on the German Society of Clinical Chemistry (DGKC) specifications. The absorbance was read at 340 nm. The following formula was applied to determine the activities of these enzymes.

CK-MB activity (U/L): $\Delta A/min \times 8095$

LDH activity (U/L): $\Delta A/min \times 1651$

2.7 SOD activity in tissues

The levels of the SOD enzyme in the tissue samples were measured colorimetrically according to previous works (21). The samples were centrifuged for 10 min at

1000 r/m, and the supernatants were discarded. Then the pellets were resuspended in PBS (1×) and manually ground in an ice-water bath to break the cells. After that, 20 µL of the sample was added to 20 µL of the enzyme working solution. Subsequently, 200 µL of the substrate solution was added to each well using a multi-channel pipette and mixed thoroughly. The mixtures were incubated at 37°C for 20 min, and the optical density was determined at 570 nm.

2.8 Lipid peroxidation analysis

According to previous investigations, the generation of MDA was measured as a lipid peroxidation index **(22)**. TBA (0.67%) and trichloroacetic acid (10%) were mixed with tissue samples and boiled for 40 min. After the samples were cooled, n-butanol and HCl were added, and the mixtures were centrifuged. Finally, the upper layer was removed to read the absorbance at 535 nm using a spectrophotometer. The following formula was applied to determine MDA levels:

The levels of MDA (M) = Absorbance/ ($1.56*10^5$ $cm^{-1}M^{-1}$).

2.9 Thiol content in cardiac tissues

According to previous protocols, the thiol content was measured by mixing 50 µL of the homogenized tissue with tris-EDTA buffer (pH = 8.6) and measuring the absorbance at 412 nm (A1). Then, DTNB was added to the mixture, and the absorbance was read after 15 min (A2), using DTNB as a blank. Thiol concentration (mM) was calculated as follows:

Thiol concentration (mM) = (A2-A1-B)*0.7)/0.05*14.

2.10 Histopathological studies

Formalin (10%) was used to fix the heart tissues, and then the samples were embedded in paraffin, cut at 3 µm thickness, and stained with hematoxylin and eosin (H&E) for the microscopic evaluation of structural alterations.

2.11 Statistical analyses

GraphPad Prism software (version 8) was applied to analyze the findings. The results are presented as mean ± standard deviation (SD). One-way analysis of variance (ANOVA) followed by the Tukey-Kramer post hoc test was used to compare the groups.

3. Result

3.1 Effect of *S. minor* and CGA on cardiac factors

The findings showed that Dox elevated the levels of LDH ($p<0.001$) and CK-MB ($p<0.001$) significantly in comparison with the control group. However, treatment with *S. minor* at a dose of 300 mg/kg significantly attenuated LDH ($p<0.01$) and CK-MB ($p<0.05$) levels. Moreover, the administration of CGA reduced these markers significantly at a dose of 40 mg/kg ($p<0.001$) (Figure 1).

3.2 Effect of *S. minor* and CGA on SOD activity, lipid peroxidation, and thiol content

As shown in Figure 2, Dox reduced SOD ($p<0.001$), while *S. minor* at a dose of 300 mg/kg and CGA at a dose of 40 mg/kg enhanced SOD activity ($p<0.01$ and $p<0.001$, respectively). MDA was measured as an index of lipid peroxidation, and our findings revealed that a cumulative dose of Dox caused an increase in MDA levels in cardiac tissues ($p<0.001$). However, treatment with the higher dose of the extract (300 mg/kg) and CGA (40 mg/kg) significantly reduced MDA levels ($p<0.01$ and $p<0.001$, respectively). Moreover, the measurement of the thiol content demonstrated that the extract and CGA inhibited Dox toxicity via the elevation of the thiol content (Dox: $p<0.001$; 300 mg/kg extract: $p<0.05$; 40 mg/kg CGA: $p<0.001$) (Figure 2).

3.3 Histopathological studies

Figure 3 shows the effect of the extract and CGA on the histological modification of cardiac samples (H&E × 200). The control group exhibits normal histological features, such as normal cardiac arrangement and no inflammatory cell infiltration. Cardiotoxicity is reported as congestion of blood vessels (blue arrows) and foci of necrotizing myocarditis, characterized by inflammatory cell infiltration (black arrows) and edema (yellow arrows). The Dox + 100 mg/kg extract group shows less congestion and inflammatory infiltration than the Dox group. The Dox + 300 mg/kg extract group shows a few focal narrow areas of degeneration with mild inflammatory cell infiltration and edema. On the other hand, treatment with CGA (Dox + 40 mg/kg CGA) resulted in only mild edema and no congestion between myocardial fibers.

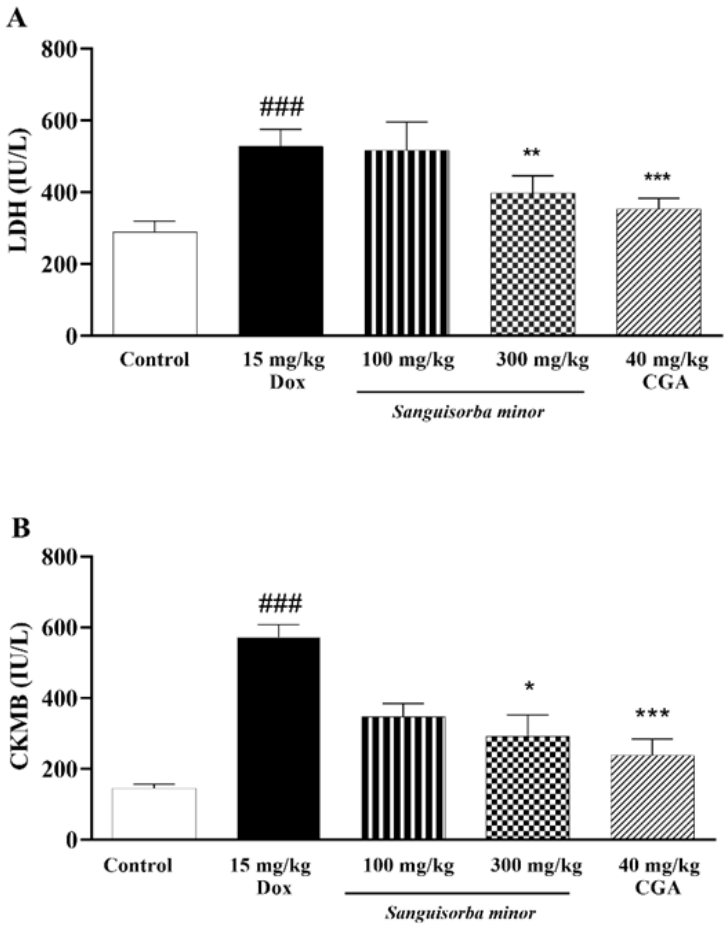

Figure 1. The effect of *S. minor* and CGA on the level of LDH **(A)** and CK-MB **(B)** after Dox administration. The levels of LDH and CK-MB were evaluated in serum samples. Data are expressed as mean ± the standard error of the mean (SEM). ### $P < 0.001$ in comparison with the control group. * $P < 0.05$, ** $P < 0.01$, and *** $P < 0.001$ in comparison with Dox (15 mg/kg). (**Prepared by Authors, 2025**).

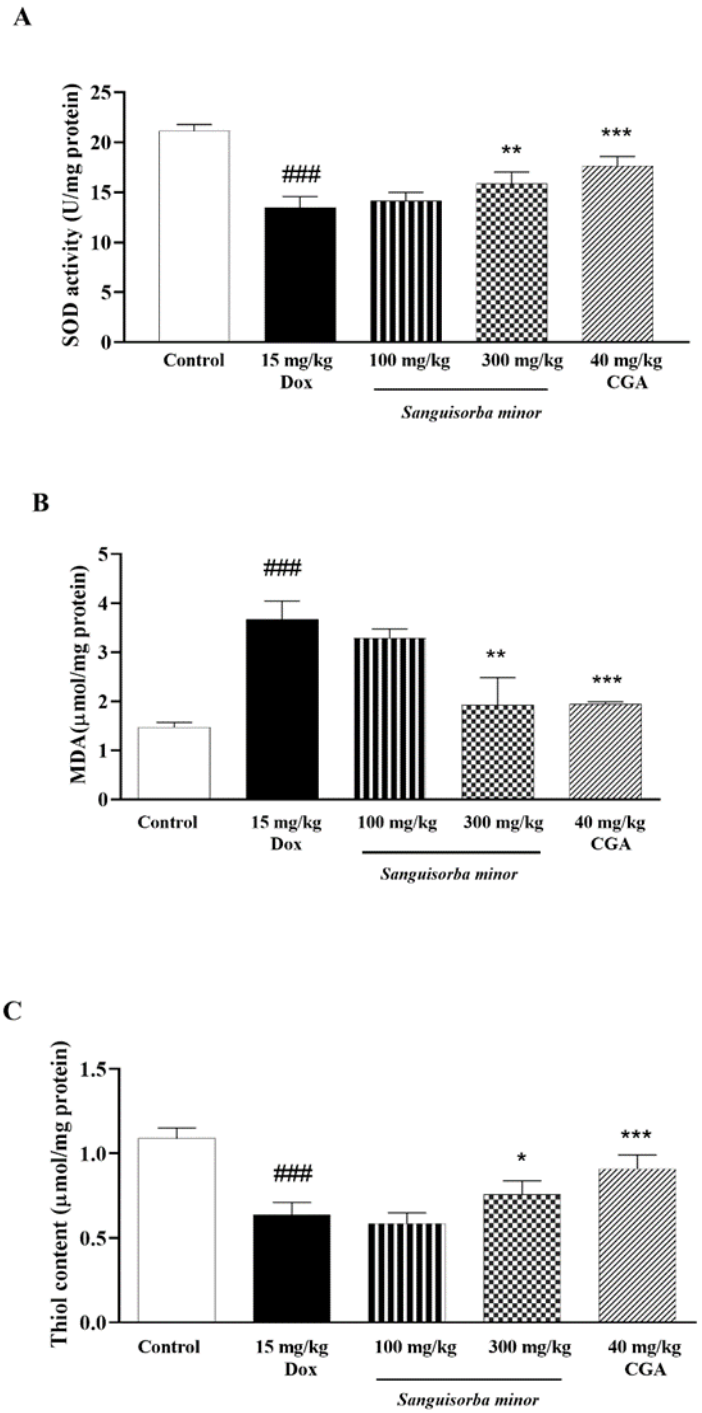

Figure 2. Effect of *S. minor* and CGA on SOD activity **(A)**, MDA levels **(B)**, and thiol content **(C)** in the heart tissue after Dox administration. Data are expressed as mean ± SEM. ### $p < 0.001$ in comparison with the control group. * $p < 0.05$ and *** $p < 0.001$ in comparison with Dox (15 mg/kg). (**Prepared by Authors, 2025**).

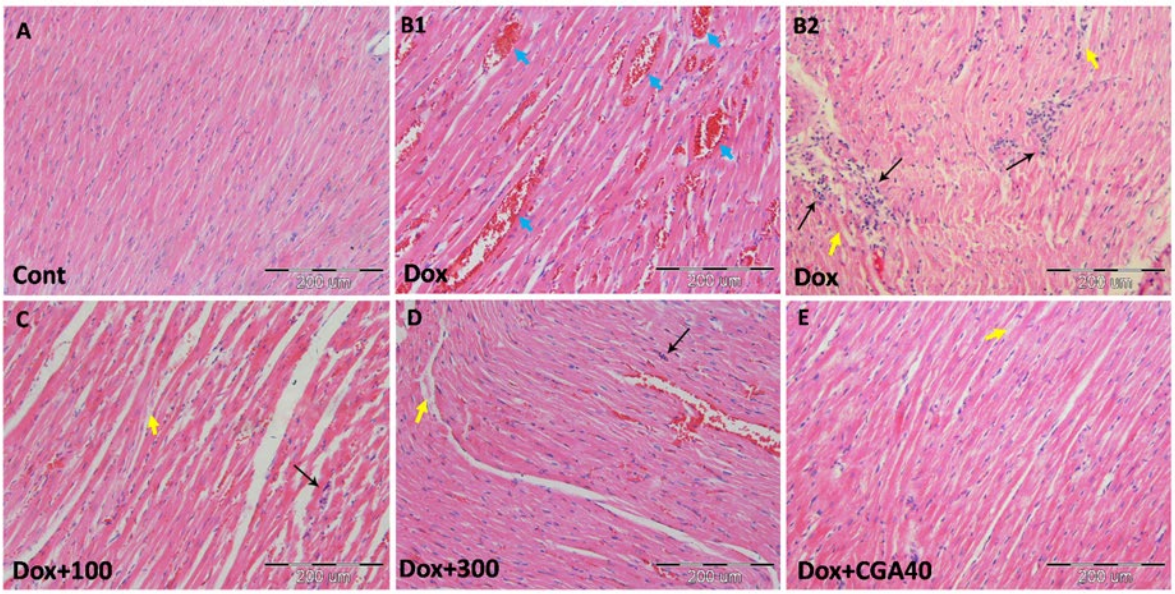

Figure 3. The effects of *S. minor* and CGA on histological changes of heart tissue in rats (200×, H&E). Control group **(A)** and Dox group **(B)**. Control group **(A)** exhibits normal histological features. Cardiotoxicity is reported as congestion of blood vessels (blue arrows) and foci of necrotizing myocarditis, characterized by inflammatory cell infiltration (black arrows) and edema (yellow arrows) in the Dox group **(B1-B2)**. The Dox + 100 mg/kg extract group **(C)** shows less congestion and inflammatory infiltration than the Dox group. The Dox + 300 mg/kg extract group **(D)** shows a few focal narrow areas of degeneration with mild inflammatory cell infiltration and edema. The Dox + 40 mg/kg CGA group **(E)** exhibits very mild edema and no congestion between myocardial fibers. (**Prepared by Authors, 2025**).

4. Discussions

In this research, our findings revealed that pretreatment with *S. minor* (100 and 300 mg/kg) and CGA (40 mg/kg), as its active ingredient, decreased Dox-stimulated cardiotoxicity. *S. minor* and CGA resulted in a decrease in MDA levels and an increase in thiol and SOD levels. The levels of CK-MB and LDH were also reduced. One of the therapeutic strategies to reduce chemotherapy-induced toxicity is the consumption of vegetables and fruits, which are rich in antioxidant compounds **(23-25)**.

Various experimental models have been used to explore the mechanisms underlying Dox-induced myocardial injury. Research indicates that oxidative stress, inflammatory responses, and disruptions in calcium homeostasis contribute significantly to the development of Dox cardiomyopathy **(26)**. In addition, Dox has been shown to interfere with DNA synthesis through intercalation into the DNA molecule **(27)**.

In line with our results, Dox leads to the elevation of cardiac enzymes, including LDH and CK-MB in serum, which is confirmed by recent studies **(15, 28)**. The administration of Dox causes ROS generation, which injures the cell membrane of cardiomyocytes and leads to the release of cardiac enzymes into the bloodstream **(29, 30)**. Leakage of cardiac enzymes leads to the rupture of the membrane **(31)**, disruption of protein function, induction of lipid peroxidation, and DNA damage **(32)**.

Our study showed that the level of MDA elevated following Dox administration, which is indicative of oxidative stress induction. This finding was confirmed by previous studies **(33, 34)**. Oxidative stress influences membrane lipids and causes aldehyde production such as MDA, which reduces cardiac contractile function **(32, 35)**. The rats that received *S. minor* exhibited significant attenuation of MDA, which is probably related to the scavenging of free radicals and inhibited lipid peroxidation. MDA attenuation has been reported in previous works **(19, 36)**. Typically, lipid peroxidation occurs following oxidative stress, a reduction in antioxidant enzymes, and a decrease in thiol content **(37)**. In this study, Dox increased MDA levels, while reducing thiol content and SOD activity as the antioxidant enzyme. These findings are related to the elevation of ROS following Dox administration, which was demonstrated by other studies **(38, 39)**. In this research, *S. minor* prevented Dox-induced oxidative damage by reducing MDA and increasing thiol content and SOD. Specifically, 300 mg/kg *S. minor* showed strong cardioprotective effects that were in line with the results of other studies. Recently, our team reported that 300 mg/kg *S. minor* reduced cardiotoxicity induced by isoprenaline **(20)**.

Moreover, 100–200 mg/kg *S. minor* reduced cognitive impairment and showed strong antioxidant activity in scopolamine and aging-induced rat brain damage **(19, 36)**.

Several models have been developed to induce Dox cardiotoxicity. These models can be categorized into short-term and long-term protocols based on the duration of drug administration. In short-term models, rats are typically administered a single dose of 10–30 mg/kg Dox,

while in long-term protocols, animals receive six injections of 2–3.4 mg/kg Dox (Total dose is 12–20 mg/kg) (27, 40). It seems that six injections of Dox every other day at 2.5 mg/kg is a common model for assessing chronic cardiotoxicity. Histological analysis revealed that this injection regimen induces myocyte vacuolization and degeneration, along with interstitial edema, mild fibrosis, and infiltration of leukocytes (41, 42).

Similarly, our histopathological results indicated that Dox leads to edema, infiltration, and necrosis in cardiac cells. Moreover, it was observed that *S. minor*, especially at the higher dose, and CGA decreased cardiomyocyte toxicity.

In our previous study, *S. minor* at a dose of 300 mg/kg resulted in milder alterations, such as slight edema and congestion, in rats treated with isoprenaline (20). CGA (100 mg/kg) also attenuated cell infiltration and hemorrhage caused by a single dose of Dox (15 mg/kg) in rats (15).

The cardioprotective effect of *S. minor* can be mediated via different agents in its extracts, such as terpenoids, flavonoids, phenols, and especially polyphenolic acids (9). Polyphenolic acids, such as CGA (3, 4-dihydroxycinnamate), are identified in many plants, including *Vaccinium angustifolium*, *Crataegus monogyna*, and *Sanguisorba minor* (12, 13). Different studies have shown the protective effects of CGA in cardiac issues, such as heart failure, myocardial infarction, hypertension, and atherosclerosis (43). CGA reduced isoprenaline-induced cardiotoxicity by stabilizing mitochondrial and lysosomal enzymes, inflammation, and oxidative stress (16, 17). Moreover, Cicek et al (15) showed that CGA decreased the cardiotoxicity of Dox via the modulation of cardiac enzymes, oxidative stress, and the elevation of Nrf2/HO-1. Our findings are confirmed by a previous study by Cicek et al (15). The difference between our work and that of Cicek et al (15) is that we injected Dox every other day, while Cicek et al (15) induced cardiotoxicity by administering Dox on the 10^{th} day. Most of the pharmacological properties of *S. minor* may be related to various compounds found in the extract, such as CGA, ellagic acid, kaempferol, catechin, and myricetin (19). Previous studies have reported the cardioprotective effects of several of these compounds against Dox, such as ellagic acid, quercetin, catechin, and kaempferol (44-49). According to the literature, the cardioprotective effect of *S. minor* can be mediated by its active compounds and the reduction of oxidative stress.

One of the plausible mechanisms underlying the observed cardioprotective effects may involve the activation of the Nrf2/HO-1 pathway, as reported in previous studies on *S. minor* and CGA (36). Since Nrf2 downregulation is a well-known contributor to Dox-induced oxidative stress and cardiomyocyte apoptosis (15, 50), its upregulation could potentially attenuate cardiotoxicity. However, Nrf2/HO-1 expression or other molecular markers were not measured in this study, and therefore, our findings should be interpreted as suggestive rather than definitive regarding the involvement of this pathway.

The present study has certain limitations, which can serve as a basis for future research. First, Dox cardiotoxicity is a multifactorial process involving oxidative stress, mitochondrial dysfunction, inflammation, and apoptosis, but our investigation focused exclusively on oxidative stress markers (MDA, SOD, thiols). Molecular endpoints, such as Nrf2/HO-1 expression or inflammatory/apoptotic mediators, which limit the mechanistic depth of our conclusions, were not measured in this study. Second, only one dose of CGA and two doses of *S. minor* were evaluated, and no dose-response analysis or extended treatment durations were performed. Third, we did not include a positive control group treated with dexrazoxane or another clinically approved cardioprotective agent, which would have provided a benchmark for comparing efficacy. Fourth, only male rats were used. This decision was made to avoid the potential confounding influence of hormonal fluctuations during the estrous cycle, which can affect oxidative stress parameters and cardiac function. Nevertheless, this limits the generalizability of our findings to female animals and human populations, and future studies should include both sexes to evaluate possible sex-specific responses. Additionally, our sample size was relatively small (n = 8 per group), and we assessed outcomes only in the short term without follow-up to determine whether the cardioprotective effects persist after treatment cessation. Finally, we did not perform functional cardiac assessments such as echocardiography or MRI; therefore, biochemical and histopathological improvements could not be directly correlated with changes in cardiac performance. Future research should address these limitations through mechanistic studies using molecular assays, evaluation of multiple dosing regimens, inclusion of sex-balanced models, and integration of functional cardiac outcome measures.

5. Conclusion

This study demonstrated that *S. minor* and CGA significantly ameliorated Dox-induced cardiotoxicity in rats by reducing MDA levels, as well as elevating thiol content and SOD activity. They could also decrease LDH and CK-MB levels. These findings suggest that the cardioprotective effects may be partially mediated through the modulation of oxidative stress, although the precise molecular pathways, such as Nrf2/HO-1 activation, inflammation, and apoptosis, remain to be confirmed. The results should be interpreted with caution, given the limited dosing regimens, small sample size, male-only animal model, and lack of functional cardiac outcome measures. Future research should address these limitations through mechanistic studies using molecular assays, evaluation of multiple dosing regimens, inclusion of sex-balanced models, and integration of functional cardiac outcome measures.

6. Declarations

6.1 Acknowledgments

The authors thank the Vice-Chancellor for Research, Mashhad University of Medical Sciences, Mashhad, Iran (grant number: 4000997) for financial support.

6.2 Ethical Considerations

This research was carried out according to the National Institutes of Health (NIH) Guide for Laboratory Animals and was confirmed by the Animal Ethics Committee of Mashhad University of Medical Sciences, Mashhad, Iran (IR.MUMS.MEDICAL.REC.1400.715).

6.3 Authors' Contributions

AH: conceptualization, design of the study, manuscript review. MSA: experimental studies, data analysis, and statistical analysis. PY: experimental studies and manuscript preparation. FT: experimental studies. All authors participated in reviewing the manuscript and its revision, and they were involved in research, interpretation, and finalizing the manuscript.

6.4 Conflict of Interest

The authors report no conflict of interest.

6.5 Fund or Financial Support

This research received no external funding.

6.6 Using Artificial Intelligence Tools (AI Tools)

The authors were not utilized AI Tools.

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How to Cite This Article:

Alavi M S, Torabi F, Yazdanpanah P, Hosseini A. Protective Effects of *Sanguisorba minor* and Chlorogenic Acid Against Doxorubicin-Induced Cardiotoxicity in Rats. J Adv Med Biomed Res. 2025;33(160):156-66.

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