

The Protective Effects of Bacosides against Doxorubicin Induced Cardiomyopathy in Rats

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Abstract: Background: Doxorubicin (DOX) is a widely used chemotherapeutic agent known for its dose-dependent cardiotoxicity. Cardiomyopathy induced by DOX is primarily mediated through oxidative stress and inflammation. Bacopa monnieri, a traditional medicinal herb, contains bacosides—saponin compounds known for their antioxidant and anti-inflammatory properties. **Objective:** This study aimed to investigate the cardioprotective potential of bacosides against DOX-induced cardiomyopathy in rats through biochemical and histopathological assessments. **Methods:** Rats were divided into three groups: a control group receiving normal saline, a DOX-treated group (2.5 mg/kg IP, and a group receiving both DOX and bacosides (200 mg/kg/day orally). Biochemical markers of cardiac injury (LDH, Troponin T, CRP) and histological changes in cardiac tissue were evaluated at the end of the treatment period. **Results:** DOX administration significantly elevated serum markers of cardiac injury and caused myocardial degeneration, necrosis, and inflammation. In contrast, rats co-treated with bacosides showed lower levels of LDH, Troponin T, and CRP, along with preserved myocardial architecture and reduced inflammatory infiltration. **Conclusion:** Bacosides exhibited a protective effect against DOX-induced cardiotoxicity, likely due to their antioxidant and anti-inflammatory properties. These findings suggest that bacosides could be considered as a potential adjunct therapy to mitigate chemotherapy-associated cardiac damage.

Keywords: Doxorubicin, Bacosides, Cardiomyopathy.

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Research Paper

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How to cite this paper:

Ahmed Hamish Al-Darraj & Anwer Sabah (2026). The Protective Effects of Bacosides against Doxorubicin Induced Cardiomyopathy in Rats. *Middle East Res J. Pharm. Sci.* 6(1): 8-14.

Article History:

| Submit: 28.02.2026 |
| Accepted: 31.03.2026 |
| Published: 04.04.2026 |

1. INTRODUCTION

Doxorubicin (DOX) is a widely used anthracycline antibiotic known for its potent antineoplastic activity against a variety of cancers, including breast, lung, and hematological malignancies. However, its clinical utility is significantly limited by dose-dependent and cumulative cardiotoxicity, which can lead to irreversible cardiomyopathy and congestive heart failure [1]. The pathophysiology of doxorubicin-induced cardiomyopathy (DIC) is multifactorial, with oxidative stress, mitochondrial dysfunction, and apoptotic signaling in cardiomyocytes being central mechanisms [2].

In recent years, natural antioxidants have garnered considerable interest as adjunct therapies to mitigate DOX-induced cardiotoxicity due to their capacity to scavenge reactive oxygen species (ROS) and modulate cellular defense mechanisms [3].

Among these, Bacopa monnieri, a traditional Ayurvedic herb, has attracted attention for its neuroprotective, antioxidant, and adaptogenic properties.

The primary active constituents of Bacopa monnieri are bacosides, especially bacoside A, which have been demonstrated to enhance endogenous antioxidant enzyme levels and protect against oxidative damage in various tissues [4].

Preclinical studies have shown that bacosides exert protective effects on cardiac tissue by reducing lipid peroxidation, restoring glutathione levels, and enhancing the activities of catalase and superoxide dismutase [5]. Although most studies to date have focused on the neuroprotective and cognitive-enhancing effects of bacosides, emerging evidence suggests that their antioxidant and membrane-stabilizing properties may also play a role in cardioprotection. In particular, their potential to counteract DOX-induced myocardial

injury in experimental models warrants further investigation.

The Aims of Study

To explore the protective role of bacosides against doxorubicin-induced cardiomyopathy in rats, focusing on biochemical, histopathological, and

functional cardiac markers, to elucidate their therapeutic potential cardioprotective agent.

2. MATERIALS AND METHOD

2.1 Materials

No.	Materials	Use
1	Insulin syringes	For drug administration
2	Syringe (3ml,5ml)	for blood collection, from the heart
3	Diethyl Ether	for anesthesia/euthanasia
4	Scalpel	for cutting skin and organs
5	Surgical Scissors	for dissection
6	Forceps	for handling tissues
7	Formalin	10% neutral-buffered for tissue fixation
8	Sterile Gloves	for hygiene and safety
9	Pipettes	For collect serum
10	Clot activator tubes (yellow gel tube)	for collect blood sample
11	Centrifuge	for separating serum from blood
12	Oral gavage needle	For drug administration

2.2 Preparation of Bacoside Extract

Bacosides were prepared from commercially available as capsule (Bacopa) from NOW company. The capsules were opened and the powder was accurately weighed to obtain the required dose. Due to the poor aqueous solubility of bacosides, the powder was dissolved in a solvent mixture consisting of distilled water and ethanol (70:30, v/v) to enhance solubility. The solution was stirred thoroughly to ensure proper dissolution and was freshly prepared each day prior to administration [6].

This method of using ethanol as a co-solvent for bacoside extraction is supported by previous studies, where ethanol (70–95%) has been shown to be effective in extracting saponin-rich fractions from *Bacopa monnieri* [7].

2.3 Administration of Doxorubicin to Induce Cardiotoxicity

Doxorubicin vials (50mg) manufactured by Kocak Pharma (Turkey) were reconstituted with 20 mL of distilled water and administered intraperitoneally at the calculated dose. Animals received a total cumulative dose of 12 mg/kg doxorubicin, administered in three divided doses given every other day. A commonly utilized protocol involves intraperitoneal (IP) injections of DOX every other day.

2.4 Experimental Groups

The rats were randomly divided into 3 group each one including 4 member, treated for 10 days into the following:

Group I (Normal Control): Received normal saline only via IP injection and oral gavage.

Group II (DOX Control): Received Doxorubicin (12 mg/kg, IP) without any treatment.

Group III (DOX + Bacosides): Received Doxorubicin as above, followed by oral Bacosides (200 mg/kg/day) for 4 weeks.

2.5 Monitoring and Evaluation Parameters

At the end of the study, experimental rats were sacrificed periodically for blood collection, chloroform was used for anesthesia. Blood was then drawn from their hearts, collected in anticoagulant tubes, and the following parameters were evaluated:

Biochemical Analysis: Blood samples were collected via cardiac puncture for serum markers of cardiac injury (e.g., Troponin-I, CRP, LDH).

Histopathology: Heart tissues were harvested, fixed in 10% formalin, embedded in paraffin for microscopic examination.

3. RESULT

The rats treated with doxorubicin alone (12 mg/kg IP every other day for 10days) showed clear signs of cardiotoxicity, including reduced activity, significant weight loss, and lethargy. Histopathological examination of cardiac tissue revealed widespread myocardial degeneration, necrosis, and inflammatory cell infiltration. In contrast, the group that received both doxorubicin and bacoside (200 mg/kg) demonstrated preserved cardiac structure, with reduced signs of cellular damage and less inflammatory infiltration. The protective effect of bacoside was evident in comparison to the doxorubicin-only group.

3.1 Parameters Evaluation

The cardiotoxic effects of Doxorubicin (DOX) and the protective role of Bacoside were assessed by measuring serum levels of LDH, Troponin T, and CRP.

LDH (U/L):

Rats treated with DOX alone (Group 1) exhibited elevated LDH levels ranging from 432.1 to 566.9 U/L, indicating cardiac cell damage. In contrast, the Doxy + Bacoside group (Group 2) showed lower LDH levels (298.5 to 443.8 U/L), suggesting a protective effect of Bacoside against DOX-induced myocardial injury.

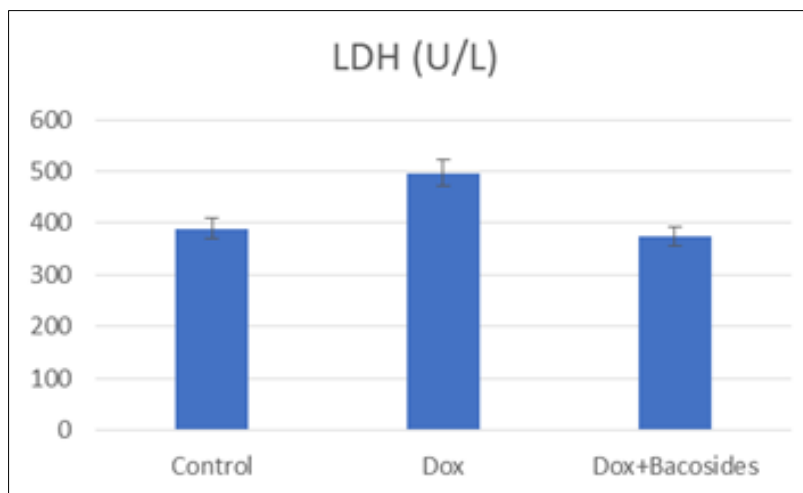


Figure 1: Effect of bacosides on serum LDH levels

This figure shows a comparison of lactate dehydrogenase (LDH) levels between the control, DOX-treated, and DOX + bacoside groups. A significant elevation in LDH is observed in the DOX group, indicating cardiomyocyte injury.

Co-treatment with bacosides reduced LDH levels, suggesting a protective effect.

Troponin T (pg/mL):

The levels of cardiac-specific Troponin T were markedly higher in the DOX-only group (522.7 to 776.2 pg/mL), confirming myocardial injury. Meanwhile, rats receiving both DOX and Bacoside showed reduced Troponin T levels (302.8 to 411.6 pg/mL), further supporting the cardioprotective role of Bacoside.

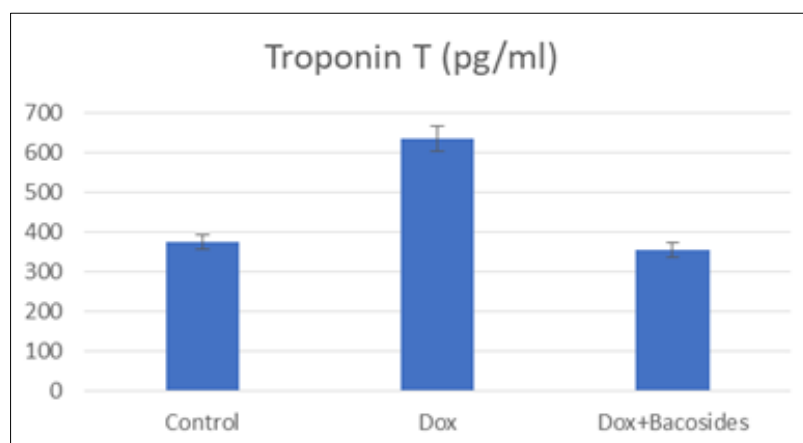


Figure 2: Effect of bacosides on serum Troponin T levels

Troponin T levels were significantly higher in the DOX group, consistent with myocardial damage. Co-administration of bacosides reduced troponin levels, indicating reduced cardiac injury.

CRP (mg/L):

Inflammatory marker CRP was slightly elevated in the DOX-only group (0.5 to 1.4 mg/L), while rats in Group 2 had lower levels (0.3 to 1.0 mg/L), indicating reduced systemic inflammation in the presence of Bacoside.

Overall, co-administration of Bacoside with DOX led to noticeable reductions in biomarkers of

cardiac damage and inflammation, indicating its potential in attenuating DOX-induced cardiotoxicity.

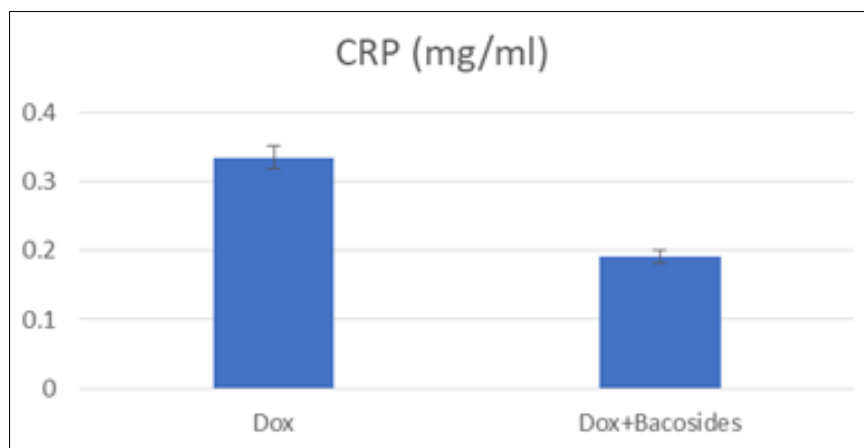


Figure 3: Effect of bacosides on CRP levels

C-reactive protein (CRP) was moderately elevated in the DOX group, reflecting systemic

inflammation. Bacoside treatment showed a reduction in CRP, demonstrating anti-inflammatory activity.

3.2 Histological Evaluations

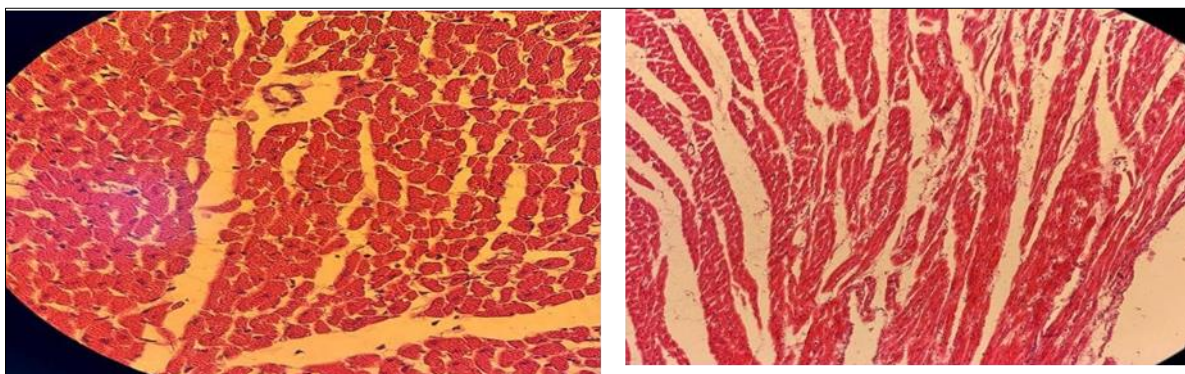


Figure 4: Histological section of cardiac muscle tissue for the control group

The image demonstrates the typical architecture of healthy cardiac muscle fibers, including branched striated fibers, centrally located nuclei, and clearly

visible intercalated discs. No pathological changes such as necrosis, inflammation, or fibrosis are observed.

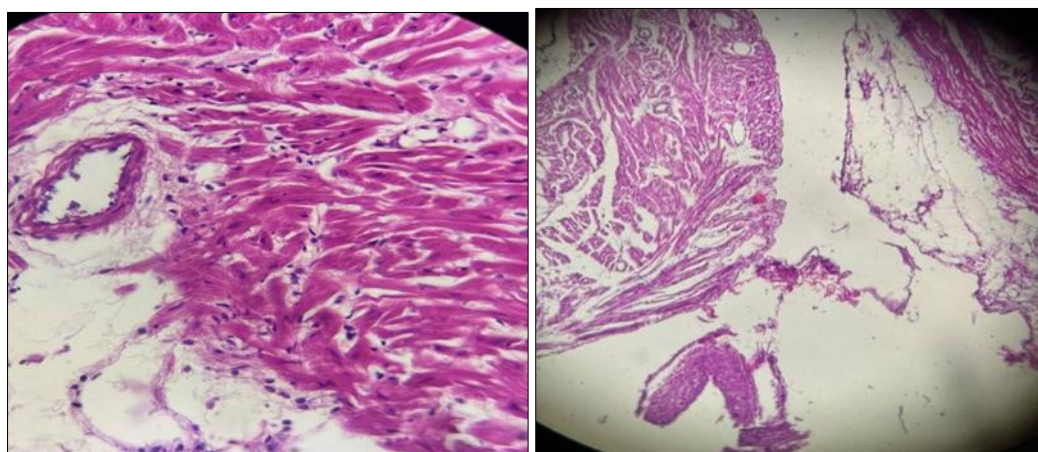


Figure 5: Histological section of cardiac tissue from the Doxorubicin

The section demonstrates prominent histopathological changes associated with doxorubicin-induced cardiotoxicity, including: Pericardial vascular congestion, as evidenced by engorged and dilated blood vessels in the pericardial region, indicating impaired vascular drainage and early vascular injury.

Interstitial edema, visualized as widened spaces between myocardial fibers due to fluid accumulation in the interstitial tissue, reflecting increased vascular permeability.

Pericardial infiltration by chronic inflammatory cells, particularly lymphocytes and mononuclear cells, indicating an ongoing chronic inflammatory response.

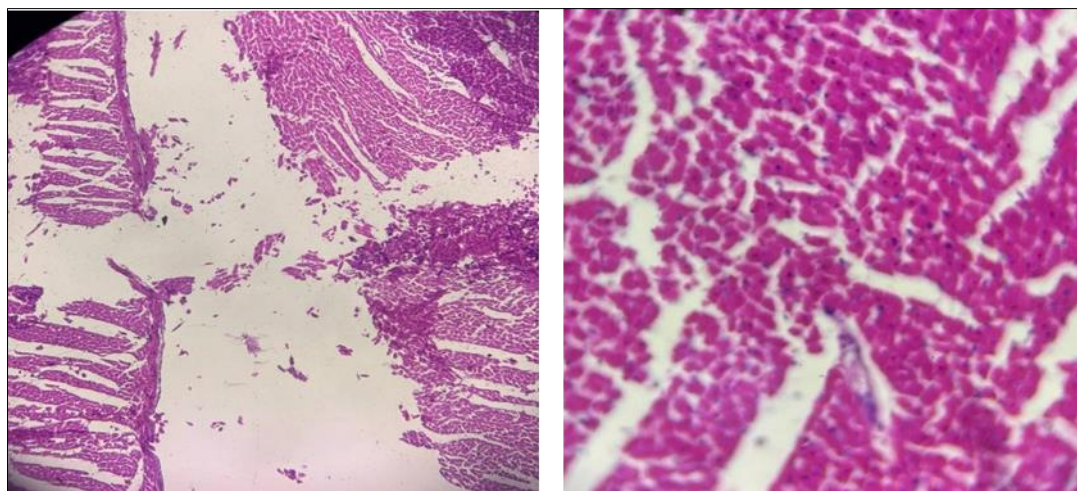


Figure 6: Histological section of cardiac tissue from the Doxorubicin + Bacopa-treated group

The image reveals signs of healing characterized by healing by fibrosis. Additionally, a reduction in inflammatory cell infiltration is observed when compared to diseased or untreated groups. These findings suggest a reparative response facilitated by the combined treatment, indicating potential anti-inflammatory and tissue-protective effects.

4. DISCUSSION

The current study investigated the protective effects of bacosides against doxorubicin-induced cardiotoxicity in rats. Doxorubicin is known for its potent chemotherapeutic effects, but its clinical use is restricted by its dose- dependent cardiotoxic profile, primarily attributed to the generation of reactive oxygen species (ROS), mitochondrial dysfunction, and the triggering of apoptotic pathways in cardiomyocytes [8].

In this study, repeated intraperitoneal injections of doxorubicin (12 mg/kg) every other day for a cumulative dose of 12 mg/kg successfully induced signs of cardiotoxicity, as evidenced by elevated serum levels of LDH, Troponin T, and CRP, along with histological evidence of myocardial degeneration, necrosis, and inflammatory infiltration. These findings align with previous literature indicating that such dosing protocols reliably mimic doxorubicin induced cardiomyopathy in animal models [9].

Co-administration of bacosides (200 mg/kg/day, orally) significantly ameliorated these toxic

effects. Rats treated with both DOX and bacosides exhibited notably lower serum levels of LDH and Troponin T, which are sensitive indicators of myocardial injury. In addition, the modest reduction in CRP levels in the co-treated group suggests that bacosides may also exert antiinflammatory effects alongside their known antioxidant activity. Histopathological analysis further confirmed the cardioprotective role of bacosides, showing preserved myocardial architecture and reduced cellular damage compared to the DOX-only group.

The protective effects of bacosides can be attributed to multiple molecular mechanisms:

Antioxidant Defense Activation: Bacosides have been shown to activate the Nrf2/ARE pathway, which enhances the expression of endogenous antioxidant enzymes such as superoxide dismutase (SOD), catalase (CAT), and glutathione peroxidase (GPx) [10]. This pathway plays a central role in cellular defense against oxidative stress induced by doxorubicin [11].

Inhibition of Apoptotic Signaling: Bacopa extracts can modulate apoptotic proteins by downregulating pro-apoptotic Bax and caspase-3, while upregulating anti-apoptotic Bcl-2, thus preventing cardiomyocyte apoptosis a hallmark of doxorubicin-induced cardiotoxicity [12].

Suppression of Inflammation: Bacosides may inhibit the NF- κ B signaling pathway, a key regulator of inflammatory gene expression. By doing so, they reduce the production of inflammatory cytokines and limit myocardial inflammation [13].

Mitochondrial Protection: Bacopa is also believed to help stabilize mitochondrial membrane potential and reduce mitochondrial ROS generation, thereby preserving mitochondrial integrity and energy production during oxidative insult [14].

The ethanol–water (70:30) extraction method used in this study effectively preserved saponin-rich fractions of *Bacopa monnieri*, especially bacosides A and B, which are believed to be the primary bioactive components responsible for these effects [15].

Importantly, no significant histological abnormalities were noted in the normal control or the bacoside-only treated group, indicating that bacosides are well tolerated at the administered dose and do not produce adverse cardiac effects when given alone. This favorable safety profile, combined with the observed cardioprotection, highlights the potential utility of bacosides as a promising adjunctive therapy to mitigate DOX-induced cardiotoxicity.

Moreover, the present findings are consistent with previous reports showing similar cardioprotective effects of natural antioxidants such as curcumin and resveratrol.

In summary, the findings of this study suggest that bacosides offer significant protection against DOX-induced myocardial injury in rats. This cardioprotection is likely mediated through their antioxidant and anti-inflammatory mechanisms. Further research is warranted to explore the molecular pathways involved, optimize dosing regimens, and evaluate the clinical relevance of these findings in larger animal models and human trials.

Based on the findings of this study, the following recommendations are proposed:

Further Studies: Conduct additional experimental studies with larger sample sizes to validate the cardioprotective effects of bacosides.

Dose Optimization: Explore various doses and treatment durations to identify the most effective and safe regimen.

Toxicity Evaluation: Assess the long-term safety of bacosides when used chronically or in combination with chemotherapeutic agents.

Clinical Translation: Encourage clinical studies to evaluate the potential of bacosides as adjunct therapy in cancer patients receiving doxorubicin.

5. CONCLUSION

This study demonstrates that bacosides, the active constituents of *Bacopa monnieri*, offer significant protection against doxorubicin-induced cardiotoxicity in rats. Administration of bacosides alongside doxorubicin led to a notable reduction in cardiac injury biomarkers (LDH, Troponin T, CRP) and preserved myocardial

tissue structure, as observed in histopathological analysis. These findings suggest that the cardioprotective effects of bacosides may be attributed to their potent antioxidant and anti-inflammatory properties.

Given their favorable safety profile and efficacy in reducing cardiac damage, bacosides may serve as a promising adjunctive therapy to mitigate the cardiotoxic side effects of doxorubicin in clinical settings. Further studies are warranted to elucidate the precise molecular mechanisms involved and to validate these findings in larger animal models and human trials. These findings support the potential use of bacosides as cardioprotective agents alongside chemotherapy in clinical practice.

6. ACKNOWLEDGEMENTS

Special thanks to Anwer Sabah for his methodological insights and for his significant role in shaping the experimental design and for his contributions to the overall success of the project

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