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Original Article

Cardio-Protective Effect of Malvidin against Doxorubicin-Stimulated Cardiotoxicity in Experimental Rat Models

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ABSTRACT

Background: Malvidin (MAL) is an anthocyanidin having therapeutic characteristics that provide several therapeutic advantages. Doxorubicin (DOX) is a valuable anti-tumor drug with a wider anticancer range; nevertheless, DOX's cardiotoxic side effects via oxidative stress and apoptosis restrict its clinical use. There are various old and modern solutions that can aid with this predicament. Even decades after the drug's side effects were revealed, no successful strategy for managing this clinical disease has been found. The goal of the present investigation is to study the cardioprotective ability of the natural compound MAL against DOX-stimulated cardiotoxicity in rat models. **Materials and Methods:** Upon induction of cardiotoxicity and administration of MAL, assessment of parameters including heart and body weight, antioxidant levels, serum lipid profile, cardiac biomarker levels and inflammatory marker levels were carried out. **Results:** It was discovered that treatment with MAL remarkably protected the mice from DOX-triggered cardiotoxicity, as evidenced by increased heart and body weight, antioxidant enzyme levels, reduced levels of cardiac biomarker levels and inflammatory parameters and improved heart morphology. **Conclusion:** Thus, MAL demonstrated to be a valuable substance for protection of cardiac tissues against DOX-stimulated cardiotoxicity.

Keywords: Anti-inflammatory, Cardiotoxicity, Doxorubicin, Malvidin, Oxidative stress.

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INTRODUCTION

Doxorubicin (DOX), also known as Adriamycin, is a potent anti-cancer medication belonging to the anthracycline antibiotic class. It is frequently utilized for treating a variety of malignancies, notably breast, liver, lymphoma, lung, ovarian tumors and leukemia.[1] The antitumor mechanism of DOX is mediated by direct disruption of DNA and interference with the activity of several enzymes required for DNA replication,[2] as well as oxidative stress and excess production of reactive oxygen species, which diminish antioxidants and boost lipid peroxidation, resulting in toxicity in both malignant and normal cells.[3]

Unfortunately, clinical application of DOX has been connected to certain major adverse consequences, including loss of appetite, nausea, fever, weight gain, vomiting, alopecia, immune deficiency, liver and kidney damage and severe cardiotoxicity.[4] Among them, the occurrence of a serious cardiomyopathy or heart failure is a life-threatening effect and is common in cancer patients.[5] Previous research found that DOX-induced cardiotoxicity triggered ROS formation, diminished glutathione levels, elevated malondialdehyde levels, contractile failure, mitochondrial dysfunction, lipid peroxidation, damaged DNA and apoptosis.[6]

As a result, research is currently concentrating on the prospect of alleviating DOX-mediated cardiotoxicity by minimizing oxidative stress and preventing apoptosis via endogenous antioxidant system stimulation.[7] While dexrazoxane is now the only chemoprotective drug to avoid and treat cardiotoxicity triggered by DOX, its usage involves a significant risk of producing hematological disorders and myelosuppression.[8] Thus, plant-based polyphenolic substances are increasingly being employed as a preventive measure against DOX cardiotoxicity, alongside traditional antioxidants. Several plant species having antioxidant capabilities have been investigated. These natural compounds included ashwagandha, 6-gingerol, curcumin, lemon balm, cranberry and rosemary, all of which were reported to reduce DOX cardiotoxicity.[9]

Malvidin is an anthocyanidin having therapeutic characteristics that provide several health advantages. Anthocyanidins are

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plant-based phenolic substances that predominantly occur in greens and fruits.[10] Malvidin has been shown to be an efficient anti-stress molecule by lowering oxidative stress.[11] It additionally exhibits anticancer characteristics and can stop the cell cycle by modulating the phosphorylation of signal transducers.[12] Moreover, it has been demonstrated to be helpful in regulating neurological illnesses, including Alzheimer's disease. Furthermore, it has been reported to inhibit the advancement of certain diseases due to their anti-inflammatory as well as antioxidant characteristics.[13] However, the compound has not yet been examined for DOX-stimulated cardiotoxic investigations.

The purpose of the present investigation is to study the cardioprotective potential of the natural compound MAL against DOX-stimulated cardiotoxicity in experimental rat models. Upon induction of cardiotoxicity and administration of MAL, estimation of parameters including body and heart weight, cardiac parameters, serum lipid levels, antioxidant levels, inflammatory marker levels were carried out.

MATERIALS AND METHODS

Chemicals and kits

Pure analytical grade Doxorubicin and Malvidin were obtained from Sigma-Aldrich for the present study. ELISA for estimation of different parameters was conducted using commercial kits.

Experimental animals

The experimental rats employed in this work were handled as per the Institutional Animal Ethics Guidelines. Wistar rats approximately ten to twelve weeks of age were kept in a clean facility with a 12 hr light/dark cycle, at 21-24°C, as well as relative humidity varying from 50-60%. They also received daily pellet meal and water. The animals were accustomed to the investigational surroundings for seven days before the research began.

Experimental plan

All of the rats were categorized into four groups of 6 rats each. Group I rats were regarded as normal; Group II animals were administered 20 mg/kg DOX for 2 weeks to induce cardiotoxicity. Group III rats received 25 mg/kg MAL orally and group IV rats were given MAL at a dosage of 50 mg/kg. Following anesthesia, the animals were sacrificed and blood sample was collected to separate the serum using centrifugation at 5000 g for 20 min. The serum was extracted, kept at -20°C and utilized for analyzing the biochemical parameters. A portion of the retrieved heart tissues were kept at -20°C for histological analysis.

Estimation of body and heart weight

Each rat was weighted before and after the experimental procedure. The rats were sacrificed after treatment and their hearts were removed to determine their heart weight. The data results were documented in order to conduct comparative investigations.

Analysis of cardiac biochemical parameters B-type Natriuretic Peptide (BNP), Creatine kinase-MB (CK-MB), Troponin T (TnT) and Lactate Dehydrogenase (LDH) Commercial assay kits (Abclonal, China) were employed to estimate the levels of LDH, BNP, TnT and CK-MB in the serum of animals under examination. The tests followed the manufacturer's typical procedures. The BNP and TnT concentrations were measured using a microplate fixed at 450 nm. The concentration was presented as pg/mL. The CK-MB and LDH concentrations were analyzed using a microplate fixed at 450 nm. The concentration was reported as ng/mL.

Estimation of lipid peroxidation and antioxidant enzymes of heart tissue

The supernatant containing homogenized cardiac tissue was tested for oxidative/antioxidant status, including Malondialdehyde (MDA), Catalase (CAT) and Superoxide Dismutase SOD levels.[14-16]

Analysis of serum lipid profile involved in cardiac injury

Serum samples were analyzed for Total Cholesterol (TC), Very Low-Density Lipoproteins (VLDL), Low-Density Lipoproteins (LDL) and High-Density Lipoproteins (HDL). The serum TC, LDL, VLDL and HDL levels were calculated using Burstein and Richmond's approach.[17,18]

Estimation of inflammatory marker levels

To assess inflammation, pro-inflammatory mediators including Interferon-γ (INF-γ) and Monocyte Chemotactic Protein-1 (MCP-1) were measured in tissue homogenate employing commercial ELISA kits (Raybiotech, Georgia) following the kit insert instructions.

Histopathological changes in heart tissue

The cardiac tissues were treated with formalin (10%), dried with ethanol and subsequently fixed in paraffin. The tissues were cut at 5 µm size with a microtome and stained with the help of Hematoxylin and Eosin (H&E). The stained slices were placed on slides and examined under the optical microscope with 40x magnification.[19]

Statistical analysis

All experimental data are represented as mean±SD (n=6). All data were analyzed using one-way Analysis of Variance (ANOVA). A Tukey's *post hoc* test for group comparison was carried out using SPSS for Windows. Differences were regarded as significant at $p<0.05$.

RESULTS

Estimation of body and heart weight

Figure 1 displays the body and heart weights of all of the animals. All of the rat groups exhibited dramatically diverse heart weights. The control Group I showed the highest heart weight, whereas Group II, which received DOX alone, displayed the lowest weight. Group IV, which received 50 mg/kg of MAL, demonstrated that the heart weight was restored before and after MAL treatment (Figure 1).

Estimation of cardiac biochemical parameters

Analysis of cardiac parameters including TnT, BNP, LDH and CK-MB was carried out in the experimental rats as shown in Figure 2. DOX-triggered cardiotoxicity in test rats led to significant increases in cardiotoxicity indicators such as TnT, BNP, LDH and CK-MB in their blood. Supplementing MAL to DOX-challenged rats prevented heart damage, as shown by lower levels of cardiac markers in their blood.

Analysis of lipid peroxidation and antioxidant status

To analyze the lipid peroxidation activity in the rats, MDA levels were estimated. The observed data demonstrated that Group II exhibited a high concentration of MDA, while the Group III showed a relatively lower concentration. The MAL administered group displayed values closest to the normal control group, illustrating the normalization of the range. After treatment with DOX and MAL, the antioxidants SOD and CAT were measured. The levels of the aforementioned antioxidants were elevated in Groups III and IV whereas their levels declined in Group II. In compared to Group III and IV showed a markedly higher concentration of antioxidants, suggesting the protective nature of MAL (Figure 3).

Assessment of serum lipid profile

The examination of serum lipid profile was conducted to investigate the inflammation in the heart of experimental rats. Serum TC, LDL and VLDL levels were reduced from Group II to IV. Group IV had identical lipid levels to the control Group I, while Group II exhibited the highest. Group III, which received MAL, noticed a significant decrease in lipid levels in comparison to Group II. HDL cholesterol levels showed a pattern that varied from prior parameters. Figure 4 reveals that Group IV showed the highest HDL-cholesterol levels relative to the normal control group. These levels decreased further in Groups III and II.

Analysis of inflammatory marker levels

The presence of inflammation was further examined through the quantification of INF-γ and MCP-1 markers. The control rodents did not express MCP-1 and very low levels of INF-γ, as noticeable from Figure 5. DOX treated group revealed a substantially higher concentration of MCP-1 and INF-γ. Conversely, Group III and Group IV exhibited a diminishing value for the same, confirming its anti-inflammatory nature.

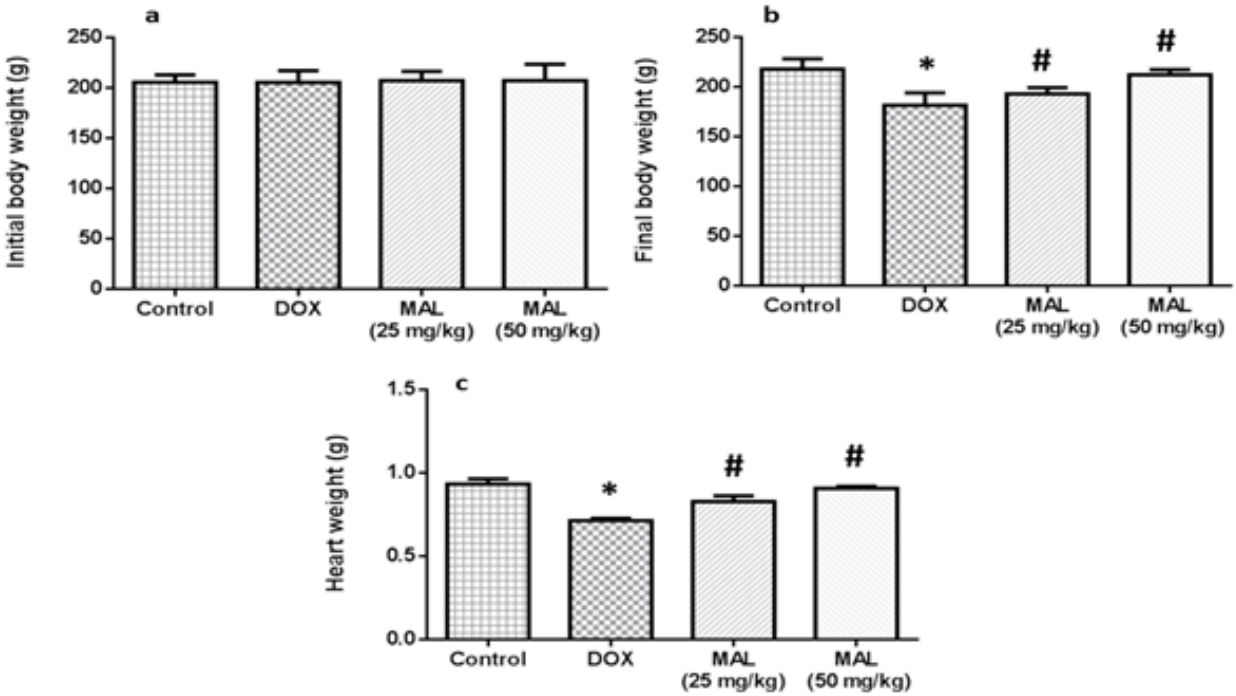

Figure 1: MAL on Initial (a) Final body (b) weight (g) and heart weight (c) by doxorubicin induced cardiotoxicity. Data are displayed as mean±SD, *p<0.05, in comparison to control group and #p<0.05, in comparison to DOX induced rats.

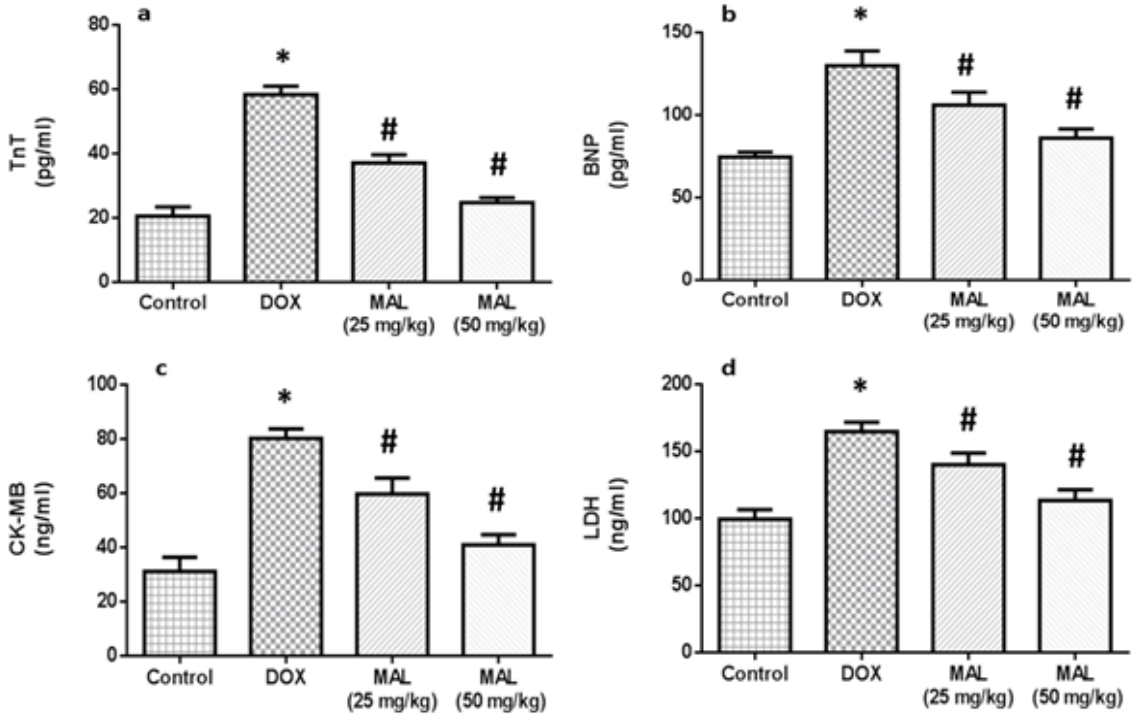

Figure 2: Cardiac parameters level on (a) TnT, (b) BNP, (c) CK-MB and (d) LDH. Data are displayed as mean±SD. *p<0.05, in comparison to control group and #p<0.05, in comparison to DOX induced rats.

Histopathological changes on Dox-induced Cardiotoxicity

The cardiac tissues in Group I rats showed the characteristic histological features. The Group II DOX-stimulated cardiac rat tissues revealed greater cardiac tissue damage, inflammatory cell infiltration and myocyte degeneration. When the lower dose of MAL was administered to Group III rats, the DOX-induced histopathological modifications in the cardiac tissues were substantially reduced. The higher dose of MAL treated rats in Group IV animals did not reveal any significant histological changes (Figure 6).

DISCUSSION

The core component for treating cancer still seems to be chemotherapy relying on DOX, but its clinical relevance and therapeutic benefit are unquestionably limited by the potentially fatal cardiotoxicity that ultimately result in ventricular dysfunction as well as congestive cardiac failure. The main contributor to DOX-induced cell injury and cardiovascular impairment is identified as uncontrollable ROS formation, causing oxidative stress to biological molecules and stimulating apoptotic pathways. The DOX-induced cardiotoxic rat model employed in this study has been reported previously[20] and the damages that were evidenced are comparable to those found by other research groups.[21]

Hence, in the current investigation, the cardioprotective impact of the natural compound MAL against DOX-stimulated cardiotoxicity in rodents has been studied. The most typical consequence associated with MI condition is a substantial decrease in both body and cardiac weight.[22,23] The cardiotoxicity-induced body and heart weight of animals decreased considerably (Figure 1). The disappearance of micro fibrils and cardiomyocytes could lead to a decline in body and heart weight. It was also noted that cytoplasmic vacuole formation caused by sarcoplasmic reticulum and T-tubule dilatation in heart tissue can result in a decreased heart weight. The reduced body weight of DOX-stimulated mice might be attributed to a decrease in intake of food caused by doxorubicin's gastrointestinal adverse effect.[24]

DOX toxicity frequently results in the accumulation of excess free radicals, which combine with oxygen molecules to produce hydroxyl radicals as well as superoxide anions.[25] DOX increases the sensitivity of cardiomyocytes to ROS by reducing the antioxidants such as CAT, GSH and SOD.[26] In the present study, the levels of antioxidants were substantially decreased in the cardiac tissues of DOX-stimulated experimental rats. In contrast, MAL-supplemented rats showed a significant improvement in the antioxidant levels in comparison to DOX-induced rats. MAL administration significantly restored all cellular antioxidants in the cardiac tissues while also significantly reducing lipid peroxidation in the DOX-induced experimental rats.[27,28]

Inflammation is an apparent consequence of doxorubicin-stimulated MI, as demonstrated in previous studies on DOX-stimulated animals. The build-up of pro-inflammatory cytokines serves an essential function in the DOX-induced

cardiotoxicity.[29] The existence of inflammation related to DOX's cardiotoxic impact was evaluated by estimating INF- and MCP-1 concentrations in the tissue homogenate of all animal groups in the research. DOX-treated rats exhibited the highest INF-γ and MCP-1 levels, signifying an inflamed heart. This level was reduced in MAL-treated animals, implying its anti-inflammatory effect. This is consistent with the outcomes of an earlier study,[30] and reveals an acute inflammation in DOX-administered rats and leukocyte aggregation in the cardiac tissues.

Modifications in the levels of LDH, Troponin-T and CK-MB are evident indications of heart damage in MI. These changes are frequently accompanied by significant increases in the ROS levels. As a result, cellular antioxidants play a vital function in preventing excessive oxidative damage in cardiac tissue. In the

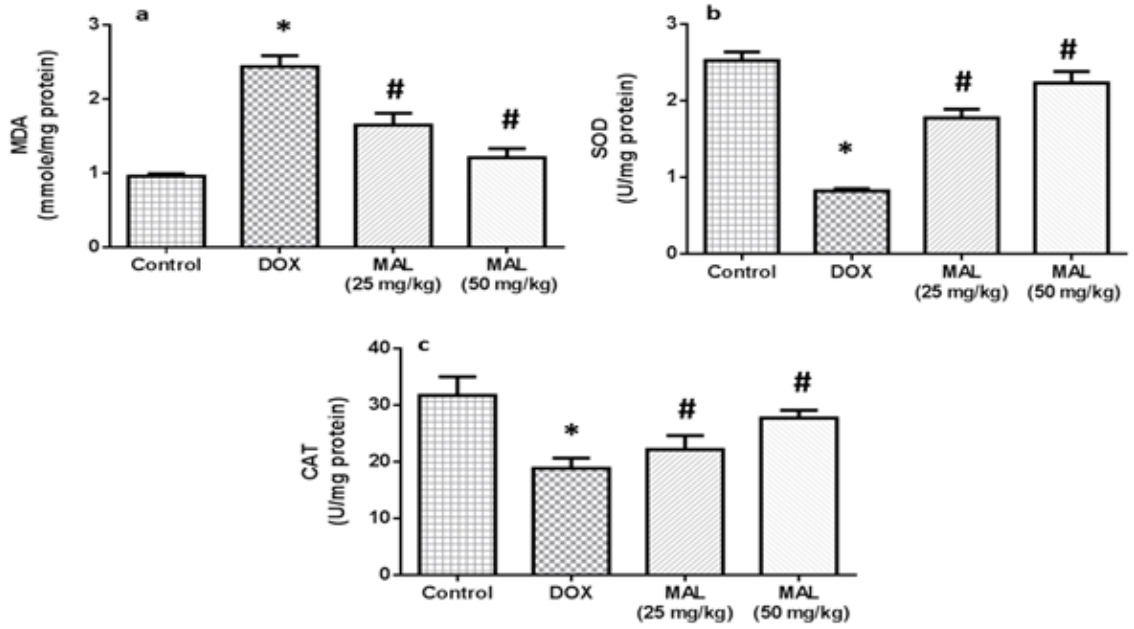

Figure 3: Lipid peroxidation and Antioxidant enzymes of heart tissue homogenate of rats on (a) MDA, (b) SOD and (c) CAT. Data are displayed as mean±SD. *p<0.05, in comparison to control group and #p<0.05, in comparison to DOX induced rats.

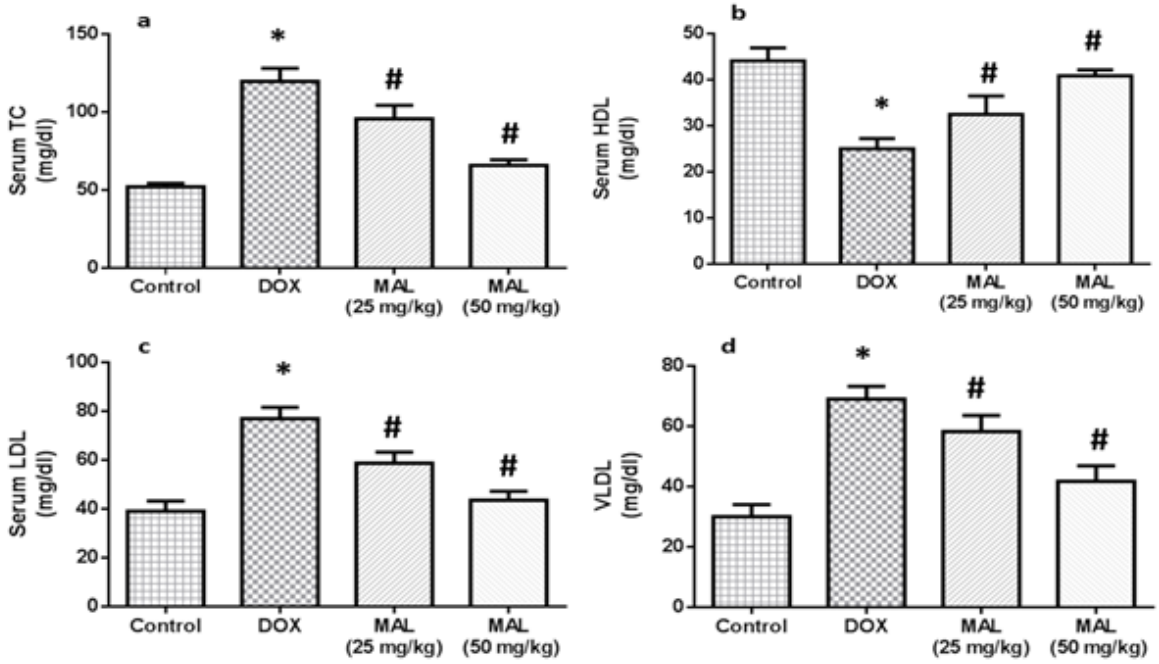

Figure 4: Serum lipid profiling and MAL index were performed to assess the inflammation present in the heart. (a) Serum TC, (b) Serum HDL, (c) Serum LDL and (d) Serum VLDL. Data are displayed as mean±SD. *p<0.05, in comparison to control group and #p<0.05, in comparison to DOX induced rats.

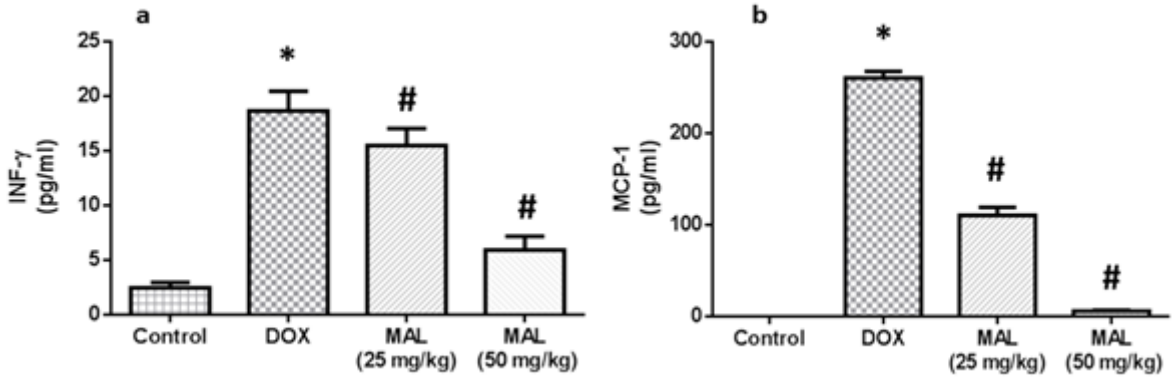

Figure 5: Effect of MAL on the inflammatory markers level in the DOX-stimulated rats. Interferon-γ (INF-γ) (a) and Monocyte Chemotacticprotein-1 (MCP-1) (b) Data are displayed as mean±SD. *$p<0.05$, in comparison to control group and #$p<0.05$, in comparison to DOX induced rats.

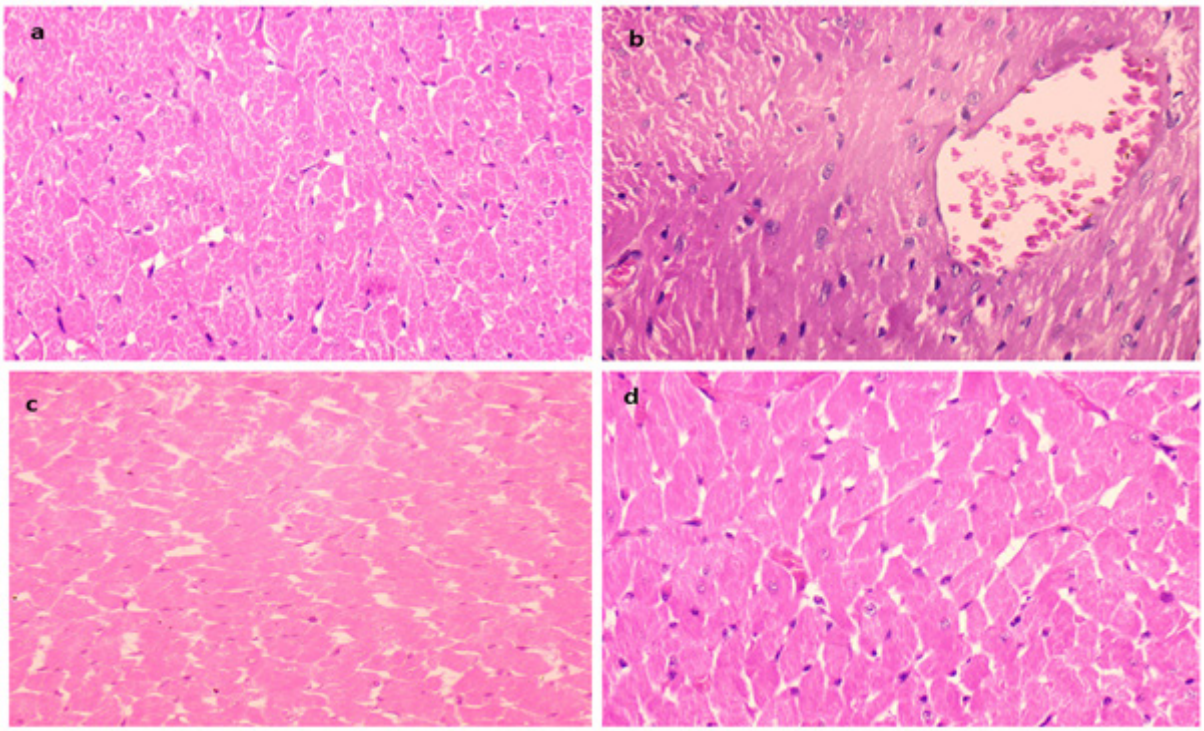

Figure 6: Histopathological Changes in Heart Tissue. Group I is normal control (a) Group II is DOX Induced (b) Group III is DOX+MAL 25 mg/kg (c) and Group IV is treatment DOX+MAL 50 mg/kg (d).

physiopathology of cardiotoxicity, CK-MB, LDH and TnT are employed as indicators for diagnosing MI.[31,22] The increased enzymatic function of LDH might be attributed to the massive buildup of ROS and their detrimental impact on the cell membrane, resulting in the release of LDH from the damaged membranes of heart cells into the bloodstream. The levels of these markers were significantly decreased upon MAL administration and these results were comparable with another investigation which employed a bioactive compound Plumbagin.[33] (Li *et al.*, 2020). In a rodent cardiotoxicity model triggered by DOX, concentrations of CK-MB and LDH increased.[34]

The study found that rats treated only with DOX displayed a disrupted lipid profile, which included elevated blood cholesterol, VLDL and LDL levels and low HDL levels. DOX administration resulted in impaired lipid and fatty acid retention.[35] MAL, in contrast, dramatically lowered blood total cholesterol levels. In addition, serum LDL and VLDL levels were decreased, while HDL levels were elevated. This demonstrates MAL beneficial involvement in hyperlipidemia prevention and subsequent cardiovascular protection. This conclusion is consistent with another study, which found that Semaglutide is

linked with substantial enhancements in cardiovascular outcomes due to an improved lipid profile.[36]

In terms of histological alterations in rat cardiac tissues, DOX treatment resulted in enhanced myocyte degeneration, infiltration of inflammatory cells and cardiac tissue destruction. The MAL-treated groups, however, did not experience these changes. Other investigations in rats have similarly shown cardiomyocyte vacuolization, absence of cross striation, collagen fiber deposition, as well as localized necrosis following DOX treatment, which is in concomitant with our findings.[37,38] MAL treatment substantially protected mice from DOX-stimulated cardiotoxicity, as noticed by increased heart weight, antioxidant enzyme levels (SOD, CAT, GSH), reduced concentrations of biomarker enzymes (CK-MB, TnT, BNP, LDH), Inflammatory parameters (INF-γ and MCP-1) and improved heart morphology.

CONCLUSION

In conclusion, MAL exhibited superior cardio-protective impact against DOX-stimulated cardiomyopathy. All previously described mechanisms of DOX-induced cardiotoxicity were investigated to determine the phytochemical's potential. MAL treatment was found to significantly protect rats from DOX-induced cardiotoxicity, as evidenced by elevated heart weight and increased antioxidant enzyme levels, decreased levels of biomarker enzymes and inflammatory parameters and improved heart morphology. Thus, the results demonstrate MAL remarkable capacity to decrease cardiotoxicity in DOX-treated animals, confirmed by the recorded data. Furthermore, a mechanistic approach to studying the drug's method of action and its ability to inhibit apoptosis in healthy cardiomyocytes is proposed. Sufficient pre-clinical experiments are planned to establish the molecule's cardioprotective properties and safety in patients receiving chemotherapy.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

ABBREVIATIONS

DOX: Doxorubicin; **ROS:** Reactive Oxygen Species; **LDH:** Lactate dehydrogenase; **BNP:** B-type natriuretic peptide; **TnT:** Troponin T; **CK-MB:** Creatine kinase-MB; **MDA:** Malondialdehyde; **SOD:** Superoxide dismutase; **CAT:** Catalase; **TC:** Total cholesterol; **ELISA:** Enzyme-linked immunosorbent assay; **VLDL:** Very low-density lipoproteins; **LDL:** Low-density lipoproteins; **HDL:** High-density lipoproteins; **INF-γ:** Interferon-γ: **MCP-1:** Monocyte chemotactic protein-1.

SUMMARY

Our investigation proved that MAL exhibited a protective impact against DOX-stimulated cardiotoxicity in animal models. It increased the body and heart weight and antioxidant enzyme levels. Their ability to decrease the levels cardiac biomarker levels and inflammatory parameters and improved heart morphology renders them a potentially valuable compound for effective protection of cardiac tissues.

ETHICAL STATEMENT

This study was approved by the Ethics Committee of Shanxi Bethune Hospital (Approval Number: LYLL-2023-002/PJ06).

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