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Maresin-1 Mitigates Doxorubicin-Induced Cardiovascular Injury in Rats By Up-Regulation of Nrf2/HO-1 Signaling Pathway

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ABSTRACT

Background: The use of doxorubicin (DOX), a broad range antitumor antibiotic, has been restricted due to the development of toxicities to important organs, such as the cardiovascular system. Maresin-1 (MaR-1) has strong pro-resolution and anti-inflammatory properties.

Objective: To demonstrate the potential underlying mechanisms and cardiovascular protective effect of MaR-1 in DOX-induced CVS damage.

Materials and methods: DOX, DOX+MaR-1, and control (10/group) were the three groups into which thirty male albino rats were divided. Assessments were made of the following: cardiac index, cardiac troponin-I (cTnI), cardiac LDH, cardiac CK-MB, serum lipid, cardiac MDA, cardiac SOD, cardiac TNF-α, cardiac IL-6, cardiac IL-10, cardiac Nrf2 gene expression, and cardiac HO-1 gene expression. Furthermore, histological and immunohistochemical examinations of the heart and aorta were carried out.

Results: Serum levels of cTnI, LDH, CK-MB, cholesterol, triglycerides, cardiac MDA, TNF-α, IL-6, and cardiac caspase-3 immunoreaction were dramatically elevated than control, while the DOX group's cardiac index value, cardiac SOD, cardiac IL-10, cardiac Nrf2 gene expression, cardiac HO-1 gene expression, and aortic ENOS immunoreaction were significantly lower. MaR-1 significantly reduced the cardiovascular alterations brought on by DOX.

Conclusion: By upregulating the cardiac Nrf2/HO-1 pathway and exhibiting anti-inflammatory, antiapoptotic, antioxidant, lipid-lowering, and anti-atherogenic properties, MaR-1 protects the cardiovascular system in DOX rats.

Keywords: Cardiotoxicity, Doxorubicin, HO-1, Maresin-1, Nrf2.

INTRODUCTION

Nowadays, one of the most popular chemotherapeutic medications for treating different kinds of cancer is doxorubicin (DOX). Despite its ability to fight tumor cells, it also damages healthy cells, such as those in the cardiovascular system **(1)**.

It was proposed that the cardiotoxicity of DOX was caused by increased apoptosis, reactive oxygen species production and disruptions in mitochondrial calcium homeostasis after treatment **(2)**. Because DOX treatment activates the innate immune system, an increasing amount of studies indicates that inflammation also be a plausible factor in DOX-induced cardiotoxicity **(3)**.

Numerous studies demonstrated that DOX treatment activates nuclear factor-kB (NF-kB), which in turn causes the expression of pro-inflammatory cytokines in cardiac tissue to increase. This leads to the development of cardiovascular illnesses and other unfavorable cardiac events. In therapeutic settings, DOX -induced cardiotoxicity mostly restricts the total dosage of DOX **(1)**. Moreover, a crucial step in the overall development of heart failure following DOX injury is cardiomyocyte apoptosis, which includes caspase-3 activation. Numerous research have shown that treating DOX-related cardiotoxicity involves identifying and creating promising therapeutic approaches that block the formation of ROS, apoptotic cell death, and the inflammatory response. The cardiotoxicity of DOX may be reduced and its clinical effectiveness enhanced with a deeper comprehension of the molecular processes. As of right now, there is no efficient way to enhance DOX-induced cardiac activity. Finding a successful treatment is still of utmost importance in this case **(4)**. Thus, it is necessary to investigate novel therapeutic molecules that permit safe dose escalation with minimal cardiotoxic effects of DOX. One important mechanism for scavenging ROS is the Nrf2/HO-1 signaling pathway. According to earlier research, lowering ROS production helps to improve the cardiomyopathy linked to DOX **(5)**.

As a cytoprotective transcription factor, Nrf2 plays a crucial part in the baseline activity and coordinated induction of antioxidant enzymes and other targeted gene products. Strategies that target Nrf2/HO-1 may have potential for treating the progression of myocardiopathy, given the critical roles that oxidative

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stress and the inflammatory response play in the pathophysiology of cardiotoxicity caused by DOX [4].

Specialized pro-resolving molecules (SPM) are a new class of bioactive compounds that includes Maresin 1 (MaR1) [6]. MaR1 was first discovered to be a lipid mediator of macrophages with pro-resolving and anti-inflammatory properties. Omega-3 fatty acids are used to make MaR1. There are protective benefits of MaR1 in models of inflammatory diseases. Although macrophages are crucial for maintaining tissue homeostasis, it is still unknown if MaR1 controls the biological activities of noninflammatory cells. In these models, MaR1 controls the expression of inflammatory cytokines, which resolves the inflammation [7].

This motivates us to carry out this research in order to examine the possible cardiovascular-protective effect of MaR-1 in DOX-induced cardiovascular damage as well as the possible underlying processes entailed in the Nrf2/HO-1 signaling pathway referral.

MATERIALS AND METHODS

30 rats (10 rats in each group) were used in this study. Thirty male Wistar albino rats weighing between 150 and 190 g were used in this study. Each pair of rats was kept in a separate cage exposing them to the normal cycles of light and dark, humidity, and room temperature. Rats were conditioned for two weeks prior to the start of the trial.

Experimental design

Rats were divided into

Group I: Control group: The vehicle-treated group received daily intraperitoneal (i.p.) injections of dimethyl sulfoxide (DMSO) for four weeks from Fisher Scientific, Loughborough, UK, and three i.p. injections of one milliliter of distilled water from days 14 to 28.

Group II (DOX): Rats were given DMSO i.p. every day for four weeks, and a total of six doses of DOX (2.5 mg/kg i.p.) three times a week from days 14 to 28 [1]. HIKMA Specialized Pharmaceuticals in Egypt supplied doxorubicin in vials under the brand name "Adricin." DOX HCL 50 mg/25 ml is contained in each vial [8].

Group III (DOX+MaR1): Rats were administered MaR1 (Cayman Chemical, Ann Arbor, MI, USA) for four weeks, with 50 mg of MaR1 [2] dissolved in 1 ml of DMSO. They also received DOX concurrently (2.5 mg/kg i.p.) three times a week from days 14 to 28. Two weeks of MaR1 administration preceded the DOX injection. They were given DOX and MaR1 with three hours interval for the next two weeks [9].

Blood samples were taken while fasting after four weeks. The rats were then sacrificed by cervical decapitation while under mild anesthesia after their ultimate body weight was determined. The hearts were then removed, weighed, and prepared for immunohistochemical evaluation, H&E histological inspection, and biochemical analysis. Additionally, the aorta was removed and prepared for immunohistochemical and histological analysis.

The cardiac index was calculated by:

Cardiac index=Organ weight/Bodyweight×100 [10].

Blood collection

All rats had blood samples taken from their retroorbital plexus. At room temperature, the blood samples were left to coagulate for half an hour. Centrifugation was used to separate the serum for 15 minutes at 3000 revolutions per minute. Prior to the experiment, the serum was frozen at -20 degrees Celsius.

Determination of serum cardiac biomarker levels and lipid profile

Utilizing the appropriate rat ELISA kits, the levels of cTnI, LDH, and CK-MB were assessed. Rat LDH ELISA Kit (Catalog No. MBS269777, MyBioSource Inc., San Diego, CA, USA), Rat cTnI ELISA Kit (Catalog Number: ab246529, Abcam, Cambridge, UK), and Rat CK-MB ELISA Kit (Catalog No. MBS2515061, MyBioSource Inc., San Diego, CA, USA) in accordance with the manufacturer's instructions. Colorimetric kits were used to measure fasting serum triglycerides (TG) and cholesterol (Biodiagnostic Company, Dokki, Giza, Egypt).

Tissue Homogenate Preparation

A tissue homogenizer was used to homogenize the weighted cardiac tissues individually. After centrifuging the crude tissue homogenate for 15 minutes at 5,000 rpm in an ice-cold centrifuge, the supernatant was collected and kept for the test at -80°C.

Following the manufacturer's instructions, the ELISA Kit was used to quantify cardiac TNF-α (Cat.: MBS2507393, MyBioSource, Sandiego, CA, USA), cardiac IL-6 (Cat.: MBS269892, MyBioSource, Sandiego, CA, USA), and cardiac IL-10 (IL-10: ERI3010-1, Assaypro LLC, Saint Charles, Missouri, USA). Following the manufacturer's recommendations, cardiac MDA and SOD were measured using calorimetric kits (Biodiagnostic Company, Dokki, Giza, Egypt).

Gene expression quantification using RT-PCR

RT-PCR was used to analyze the relative mRNA levels of the cardiac Nrf2 and HO-1 genes. The TRIzol reagent (Invitrogen, Carlsbad, CA, USA) was used to extract total RNA from cardiac tissues in accordance with the manufacturer's instructions. The extracted RNA was stored at -80^{o} C until it was needed. In the first PCR step, complementary DNA (cDNA) synthesis (reverse transcription phase) was carried out using ThermoScript RT reagent kits (Invitrogen). cDNA was then amplified using SYBR Green Mix kits (Stratagene-USA). Each amplification curve's cycle threshold, or Ct, values were determined. The reference gene was GAPDH.

GAPDH primers sequence was:

(1) Forward primer:
5 - GTCTCCTCTGACTTCAACAGCG-3.

(2) Reverse Primer:
5 - ACCACCCTGTTGCTGTAGCCAA-3.

Data analysis was conducted using the 7500 ABI PRISM 2.0.1 version (Applied Biosystems-USA). Using the comparative ΔΔCt method, Nrf2 and HO-1 relative quantification and gene expression were carried out.

The following primers were used for the Nrf2 gene:

(1) Forward primer:
5- GGTTGCCCACATTCCCAAATC-3
(2) Reverse primer:
5- CAAGTGACTGAAACGTAGCCG-3

The following primers were used for the HO-1 gene:

(1) Forward primer:
5-AGGTGCACATCCGTGCAGAG-3
(2) Reverse primer:
5-CTTCCAGGGCCGTATAGATATGGTA-3.

Histopathological Method

Sections of tissue from the heart and aorta were preserved in 10% neutral buffered formalin for histological investigations. They were then dried in ethyl alcohol, washed in xylol, and lastly preserved in paraffin. Haematoxylin and Eosin was used to stain the 4 μm-thick sections.

Immunohistochemical Method

Paraffin slices of the heart and aorta (4 μm) were incubated for 10 minutes at room temperature with 3% hydrogen peroxide. After 30 minutes of blocking with BCA solution, the aorta was probed with anti-ENOS (1:1000, mouse monoclonal, Abcam ab76198), and the heart was probed with the primary antibody anti-caspase-3 (1:100 dilution, Elabscience Corp., Wuhan, China).

Ethical approval

The Guide for the Care and Use of Laboratory Animals was followed in the execution of all experimental procedures and methodology. The experimental procedure was approved the Menoufia University Faculty of Medicine Ethics Committee with IRB NO: 4/2025ANAT5**.**

Statistical analysis

Following data collection and analysis, they were found to satisfy the parametric assumptions based on the results of the Shapiro-Wilk test. As a result, one-way ANOVA and post hoc Bonferroni's tests were applied to the data. The data were displayed using the mean ± SD. Significance was considered to exist when the p value was 0.05 or less. The data were analyzed using Graph-Pad Prism software (version 9.3.1, San Diego, CA, USA).

RESULTS

Serum levels of cTnI, LDH, CK-MB, cholesterol, triglycerides, cardiac MDA, TNF-α, and IL-6 were significantly higher than those of the control group, in contrast, the DOX group's cardiac index value, cardiac SOD, cardiac IL-10, cardiac Nrf2 gene expression, and cardiac HO-1 gene expression were significantly lower. Serum cTnI, serum LDH, serum CK-MB, serum cholesterol, serum triglycerides, cardiac MDA, cardiac TNF-α, and cardiac IL-6 were dramatically lower in the DOX+MaR1 group than in the DOX group, while cardiac index value, cardiac SOD, cardiac IL-10, cardiac Nrf2 gene expression, and cardiac HO-1 gene expression were significantly higher (Table 1).

Table (1): The measured cardiac index, serum cTnI, serum LDH, serum CK-MB, serum cholesterol, serum triglycerides, cardiac MDA, cardiac SOD, cardiac TNF-α, cardiac IL-6, cardiac IL-10, cardiac Nrf3 gene expression and cardiac HO-1 gene expression in all studied groups

	Control group	DOX group	DOX+MaR1 group
Cardiac Index	0.76±0.03	0.43±0.02 *	0.53±0.02 *#
Serum cTnI (pg/mL)	23.1±1.9	35.6±1.97*	28.9±0.6 *#
Serum LDH (U/L)	35.8±2.3	75.9±2.25 *	47.9±2.19 *#
Serum CK-MB (pg/mL)	22.9±1.14	135.2±6.58 *	76.25±3.15 *#
Serum Cholesterol (mg/dL)	90.5±2.3	210.5±2.5 *	170.6±4.1 *#
Serum Triglyceride (mg/dL)	42.1±2.3	110.2±3.15 *	80.6±1.12 *#
Cardiac MDA (nmol/ gm. Tissue)	6.32 ±0.98	22.35± 1.3*	14.56± 1.2*#
Cardiac SOD (U/gm. Tissue)	6.35 ±0.07	2.36±0.29*	4.89±0.19*#
Cardiac TNF-α (pg/ml)	19.89±4.69	189.15±2.45*	155.8±4.28*#
Cardiac IL-6 (pg/mL)	160.28±4.9	277.6±6.35*	199.8±4.45*#
Cardiac IL-10 (ng/mL)	20.25±0.89	9.88±0.95*	14.9±0.39*#
Cardiac Nrf2 gene expression	1	0.42±0.03*	0.75±0.09*#
Cardiac HO-1 gene expression	1	0.38±0.04*	0.68±0.05*#

* Significant compared with control, # Significant compared with DOX.

Histological results:

H&E:

1. Histological examination of myocardial sections of the control group (A) revealed branching anastomosing acidophilic cardiac muscle fibers. The DOX group (B) displayed a wide separation of the cardiac myofibers with inflammatory cells and interstitial bleeding. The DOX+MaR-1 group (C) demonstrated apparent improvement in the appearance of the cardiac myofibers with mild inflammatory cells (Fig.1).

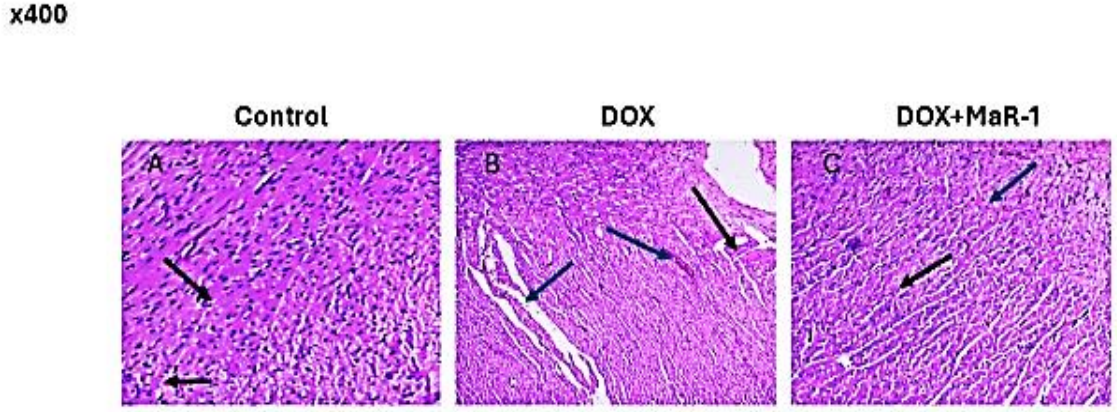

Fig. (1): (A) H&E sections of the cardiac tissue of control group showing normal branching anastomosing acidophilic cardiac muscle fibers (black arrows). (B) DOX group showing wide separation of the cardiac myofibers (black arrow) with inflamatory cells (blue arrows) and interstitial hemorrhage (green arrows). (C) DOX+MaR-1 group showing apparent improvement in the appearance of the cardiac myofibers (black arrow) with mild inflammatory cells (blue arrow). (H & E X 400).

2. Histological examination of aortic sections of the control group (A) Normal tunica intima, tunica media, and tunica adventia. (B) DOX demonstrated intimal discontinuity & degeneration along with fat accumulation, the development of foam cells, and an inflammatory response in the tunica adventitia. (C) The three aortic tunicas' normal histology was restored in the DOX+MaR-1 group, although the tunica adventia was still exhibiting an inflammatory response (Fig. 2).

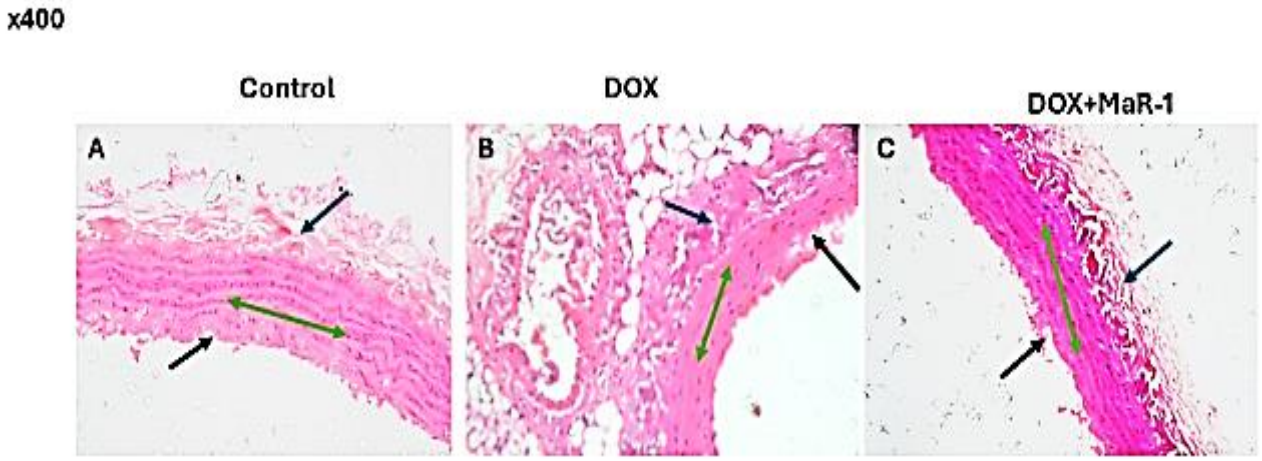

Fig. (2): H&E sections of the aorta of **(A)** control group showed normal tunica intima (black arrow), tunica media (double headed arrow) and tunica adventia (blue arrow). (B) DOX showing intimal discontinuity & degeneration (black arrows) with fat deposition, foam cells appearance and inflammatory reaction in the tunica adventia (blue arrow). (C) DOX+MaR-1 showing restoration of the normal histology of the three tunicas of the aorta but there was still inflammatory reaction in the tunica venticia (blue arrow).

Immunohistochemical results

-In sections stained by caspase-3 Ab and ENOS Ab, positive cells showed cytoplasmic brown deposits. Comparing the DOX to the control, the percentage area of caspase-3 increased significantly (72.5 ±0.21 vs. 8.06.5 ±0.31, respectively, $p<0.05$). However, compared to the DOX group, this percentage dramatically declined in the DOX+MaR-1 group (34.2±0.01 vs. 72.5±0.21, respectively, $p<0.05$). (Fig. 3: A-D).

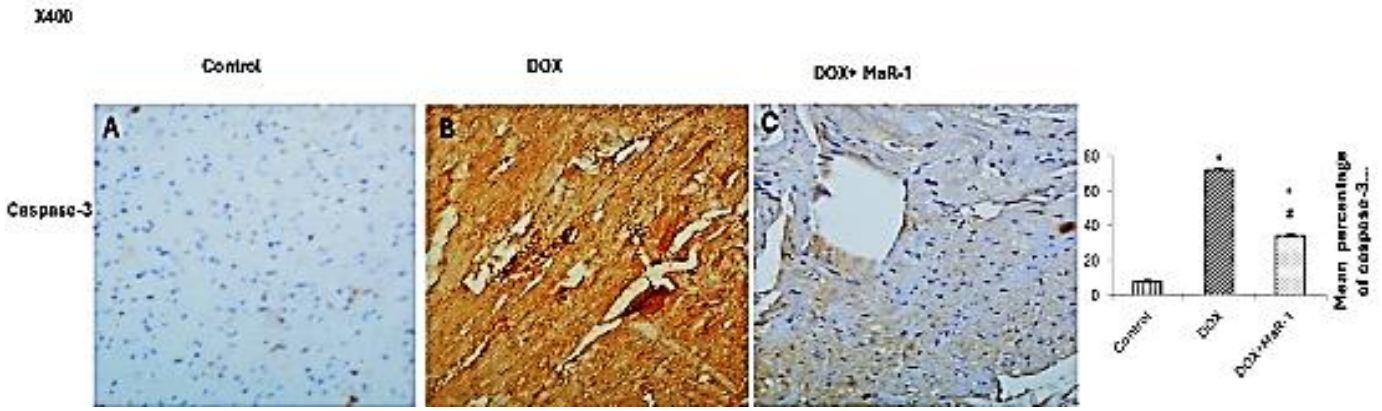

Fig. (3): Micrographs of the different groups showing a substantial elevation of the caspase-3 (A-D) immunoreaction in the DOX group and a substantial downregulation in the DOX+MaR-1 group.

When compared to the control group, the DOX group's percentage area of ENOS decreased significantly (20.5.8±0.55 vs. 80.11±0.33, respectively, $p<0.05$). However, compared to the DOX group, this percentage dramatically increased in the DOX+MaR-1 group (54.24±0.15 vs 20.58±0.55, respectively, $p<0.05$) (Fig. 4: A-D).

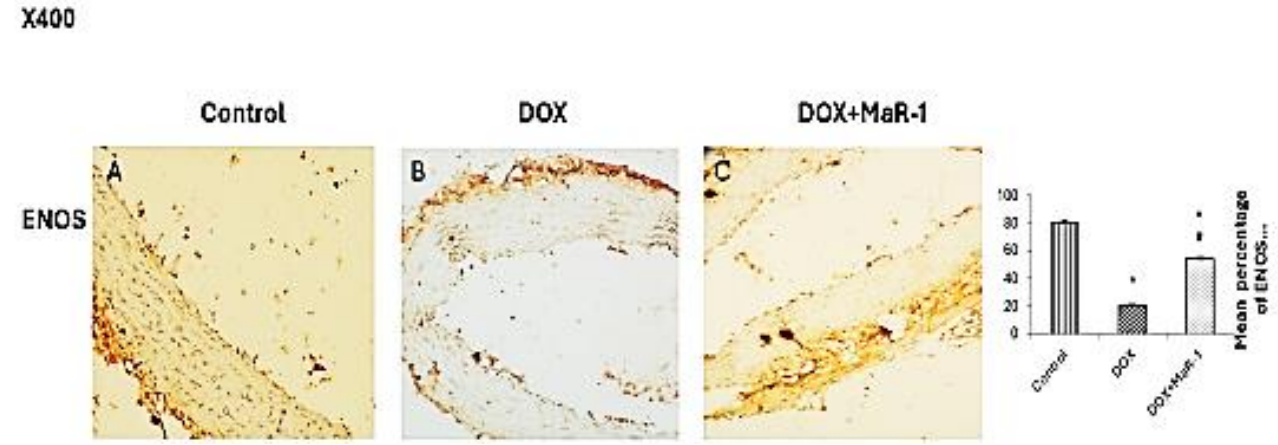

Fig. (4): Micrographs of the different groups showing a substantial downregulation of the ENOS (A-D) immunoreaction in the DOX group and a substantial elevation in the DOX+MaR-1 group.

DISCUSSION

A powerful anthracycline derivative, DOX is used to treat a wide range of human malignancies. Nevertheless, it has a lot of negative consequences, primarily severe dose-dependent cardiotoxicity. As a result, DOX must be closely monitored throughout therapeutic delivery in order to reduce cardiotoxicity [(11)].

The injection of DOX caused cardiotoxicity in the current study. Significant increases in serum levels of cardiac enzymes were indicative of cardiotoxicity, which was verified by histological and immunohistochemical analyses. Our study's data demonstrated that DOX-induced cardiotoxicity in rats was linked to markedly higher blood levels of the enzymes cTnI, LDH, and CK-MB as well as significantly lower cardiac index values when compared to the control group. Increased levels of cTnI, LDH, and CK-MB indicate that these substances are leaking into the bloodstream from damaged cardiomyocyte membranes and have been demonstrated to be a sign of cardiotoxicity [(12)].

This study clarifies the underlying molecular pathways and investigates the cardioprotective effect of MaR-1 against DOX-induced cardiovascular damage. In contrast to the DOX group, MaR-1 led to significantly lower cardiac enzyme levels and higher cardiac index values. Our findings were confirmed by our histological analysis. This is consistent with earlier research that showed MaR-1 protects against DOX-induced cardiomyocyte damage by triggering the Focal Adhesion Kinase (FAK)/AKT pathway. It's interesting to note that MaR-1 did not lessen DOX's effectiveness in cancer cells, indicating a twofold advantage in onco-cardiology [(13)].

According to earlier research, MaR1 uses the RORa/IGF-1/PI3K/Akt pathway to cause cardiomyocyte hypertrophy. MaR1 may be a crucial mediator that coordinates the resolution of inflammation with cardiac healing because it is a strong resolving factor [(7)].

When compared to the control, the DOX's data showed a substantial increase in blood cholesterol and TG. These outcomes have been consistent with earlier findings that have been published [(10)]. Our

histopathological evaluation of aorta validated our results. The downregulation of aortic ENOS immunoreaction confirmed the intimal ulceration and inflammatory infiltration found in the H&E of the DOX group's aorta. According to a prior study, DOX therapy raised the atherogenic index [14].

In comparison to DOX, treatment with MaR-1 showed a substantial improvement in the lipid profile and histological assessment of the aorta, as well as a decrease in the aortic ENOS immunoreaction. This could be explained by MaR1's capacity to inhibit inflammatory responses while simultaneously fostering the body's healing process [7]. One of the prominent metabolites of omega-3 fatty acids that exhibits a number of potent anti-inflammatory properties in inflammatory disorders is MaR1 [15].

MaR1 supports the direct mediation of macrophage function in vascular disease control. MaR1 administration caused a change in the macrophage profile toward a reparative phenotype during the development of atherosclerosis, which helped to establish an environment that restored homeostasis for plaque stability [16].

One of the ways that DOX has a cytotoxic effect is by the production of reactive species. The heart's high energy needs and high mitochondrial density make it more vulnerable to DOX-induced lipid peroxidation and damage. Additionally, the heart lacks the antioxidant enzymes required to detoxify hydrogen peroxide and superoxide anions. As a result, the produced free radicals build up and cause severe lipid peroxidation, which causes the endoplasmic reticulum, nucleic acid, and mitochondrial membranes of the heart cells to be extensively destroyed [17].

Regarding DOX's impact on the oxidative status in this investigation, DOX significantly raised the level of MDA while significantly lowering the level of SOD. The capacity of DOX to interact with cellular macromolecules is thought to be the primary mechanism of its participation in oxidative damage [18].

MaR-1 significantly reduced DOX-induced oxidative stress in the heart. In mice given LPS, a prior study found that MaR1 increased antioxidant indicators and reduced oxidative stress. Additionally, by boosting the protein expression of Nrf2 and HO-1, MaR1 therapy decreased LPS-induced cardiac cell death. By reducing OS and inflammation in response to LPS, MaR1 can protect the heart [19].

In several tissues, including the heart, DOX -induced innate immune activation triggers the release of inflammatory cytokines. Numerous investigations have shown a close correlation between DOX -induced cardiotoxicity and DOX -induced cardiac inflammation [20]. By increasing the expression of inflammatory cytokines, Dox triggers NF-kB activation to encourage myocardial inflammation [21]. Our DOX group results confirmed that, as evidenced by a decrease in the anti-inflammatory IL-10 level and an increase in pro-inflammatory cytokines.

The inflammatory condition brought on by DOX was significantly reduced by MaR-1. In a prior work, MaR1 significantly decreased TNF-α-induced monocyte adhesion, ROS production, and pro-inflammatory mediator release in cultured human vascular endothelium by up-regulating cAMP and down-regulating NF-κB activation [22]. These findings imply that MaR1 may also provide protection against atherosclerotic responses in a manner that is dependent on smooth muscle cells and/or vascular endothelium, thus decreased the production of proinflammatory cytokines [23].

One of DOX's potential mechanisms of cardiotoxicity has been linked to increased cardiomyocyte apoptosis [24]. According to **Pointon *et al.*** [25]**,** the primary mechanism of DOX cardiotoxicity is through the electron transport chain (ETC) being damaged or inhibited, which results in ATP depletion and caspase-3 activation, which starts the apoptotic degradation phase. Consistent with these preliminary findings, DOX increased cardiac caspase-3 immunoreactivity in comparison to control, which led to significant cardiomyocyte apoptosis.

In contrast to the DOX group, MaR-1 decreased the cardiac caspase-3 immunoreaction. According to a previous study, MaR1 lowered the expression of the apoptotic protein caspase3 hence lowering the apoptotic rate of cardiomyocytes. These findings suggest that MaR1 protects the heart by preventing the death of cardiomyocytes [19].

One important mechanism for scavenging ROS is the Nrf2/HO-1 signaling pathway [5]. The antioxidant system is regulated by Nrf2 and its downstream HO-1. By directly blocking the cytokines storm, inflammasome activation, and pyroptosis, Nrf2/HO-1 signaling has been shown to control antioxidation and anti-inflammation. Doxorubicin-induced cardiotoxicity was prevented by Nrf2/HO-1 signaling activation [26].

According to the data from the current investigation, DOX by itself inhibited the Nrf2/HO-1 pathway in comparison to the control. These findings are consistent with earlier research [5].

Activating Nrf2 can protect cardiomyocytes by lowering ROS and, as a result, lowering the mitochondrial apoptotic pathway in doxorubicin-induced cardiomyopathy [27]. In contrast to the DOX group, MaR-1 increased the expression of the cardiac Nrf2/HO-1 gene. In a prior work, MaR1 reverses hypertensive vascular remodeling by partially acting as a Nrf2 activator in the regulation of pyroptosis [26].

CONCLUSION

By upregulating the cardiac Nrf2/HO-1 pathway and exhibiting anti-inflammatory, antiapoptotic, antioxidant, lipid-lowering, and anti-atherogenic properties, MaR-1 protects the cardiovascular system in DOX rats.

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