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RESEARCH ARTICLE
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Potential protective effect of pitavastatin against doxorubicin-induced cardiotoxicity in male rats

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ABSTRACT

Pitavastatin is a synthetic HMG-CoA reductase inhibitor that differs pharmacologically from other statins in a number of ways because of its cyclopropyl moiety. The expression of lipoprotein lipase is higher at low doses than that of other statins, and cholesterol synthesis is inhibited at lower doses than other statins. These effects include notable long-lasting high-density and apolipoprotein A1-raising activity. Compared to other statins, pitavastatin has the highest bioavailability, about (60%) and the majority of this portion is eliminated unchanged in the bile. following oral administration. Doxorubicin-induced cardiotoxicity or heart failure have a number of potential mechanisms. After doxorubicin administration, cardiac muscle cell injuries are primarily caused by the production of free radicals, increased lipid peroxidation and ROS production in cardiac tissues are the first symptoms of dox-induced cardiotoxicity. Reactive oxygen species are promoted by aglycones and their anthracycline iron complexes. Doxorubicin stimulates both the pathways for extrinsic as well as intrinsic apoptosis. These pathways result in the apoptosis of cells in cardiac muscles due to an imbalance between oxidant and anti-oxidant molecules. Doxorubicin decreased cell viability and stimulated an inflammatory response, as evidenced by an increase in levels of the cytokines interleukin-1 beta, interleukin-6, and tumor necrosis factor-alpha. 28 male rats were divided into four equal groups at random. The rats were allowed to consume water and food in the control group. The rats in the DMSO group were given 10 ml/kg/day of DMSO orally for two weeks. For two weeks, rats in the doxorubicin group (mediated group) gained 2.5 mg/kg of the medication three times per week. Pitavastatin group: Pitavastatin was given orally over the course of two weeks at a rate of 0.64 mg/kg/day. Tumor necrosis factor, interleukin-1β, malondialdehyde, and caspase-3 levels significantly increased ($P<0.05$), demonstrating that doxorubicin induced cardiotoxicity, as well as a significant decrease in Bcl-2 levels in cardiac tissues and total antioxidant capacity of treated rats when compared to the DMSO and control groups. Pitavastatin significantly reduces the cardiotoxicity brought on by doxorubicin ($P< 0.05$), as demonstrated by a drop in inflammatory markers like tumor necrosis factor-α and interleukin-1β. The total antioxidant capacity was significantly higher ($P< 0.05$) in the pitavastatin group versus the doxorubicin-only group, the oxidative marker MDA was also markedly decreased ($P< 0.05$) in cardiac tissue. Pitavastatin significantly reduced the cardiotoxicity that the chemotherapy drug doxorubicin caused in rats. This was most likely accomplished by

interference with the apoptotic pathway, inflammation, and oxidative stress. This research sought to determine whether pitavastatin might provide protection against the cardiotoxicity that doxorubicin causes by blocking pathways that promote oxidative stress, inflammation, and apoptosis.

Keywords: *Pitavastatin, doxorubicin-induced cardiotoxicity, inflammatory factors, apoptosis markers and oxidative stress*

INTRODUCTION

Cardiotoxicity means a condition where the cardiac electricity or muscle systems are damaged and become dysfunctional. The heart weakens and loses some of its ability to pump blood as it ages. Radiation therapy, chemotherapy (the anthracycline class is a common example), anorexia nervosa complications, exposure to heavy metals, long-term cocaine use, high doses of some stimulants like cocaine, or improperly administered medications like doxorubicin can all cause cardiotoxicity (Tamargo, Caballero, and Delpón 2022). The signs and symptoms of myocardial dysfunction can range from mild to severe, including death or chronic heart failure. Cardiotoxicity can manifest in a variety of ways, from slight changes in blood pressure to arrhythmias and cardiomyopathy (Mudd Jr, Khalid, and Guddati 2021). Cardiotoxicity is a side effect that some fear will restrict the use of anthracyclines in clinical settings. Regardless of their prognosis, it might affect the survival and quality of life of cancer patient (Cardinale, Iacopo, and Cipolla 2020). Doxorubicin (Dox) has been connected to cardiac toxicity and is frequently utilized in the treatment of solid tumors like breast cancer, leukemia, and lymphoma (Babaei et al. 2020). Oxidative stress and cardiomyocyte loss caused by apoptosis are listed as the primary causes of cardiomyopathy brought on by Dox. Sarcoplasmic Reticulum depletion one of the early events in the Dox-induced cardiac dysfunction is Ca2+. Ca2+ and calmodulin-dependent kinase II level fluctuations are closely related to the apoptosis of cardiac cells and heart failure (Rawat et al. 2021). Additionally, it is believed that topoisomerase II inhibition reduces the amount of mitochondrial biogenesis, which primarily activates cell death pathways and results in Dox-mediated cardiotoxicity. Also known to play significant roles in Dox-induced cardiotoxicity are mitochondrial dysfunction, an alteration in an autophagy, nitric oxide release, inflammatory mediators, calcium dysregulation, iron regulatory protein, and cell death. Another crucial element in this procedure is reactive oxygen species (ROS) (Kalyanaraman 2020). DOX anti-cancer effect is primarily mediated in rapidly expanding tumors by DNA intercalation and topoisomerase II inhibition. DOX, however, limits its therapeutic use because it increases the risk of cancer patients dying by accumulating and dose-dependent cardiotoxicity (Renu et al. 2018). Pitavastatin is a highly a powerful inducer of the hepatocyte 3-hydroxy-3-methylglutaryl-CoA (HMG-CoA) reductase and inducer of the hepatocyte low-density lipoprotein-cholesterol (LDL-C) receptor compared to other statins (Bouitbir et al. 2020). Many neurodegenerative disorders, as well as epilepsy and seizures, have been linked to oxidative stress and mitochondrial dysfunction. Pitavastatin significantly reduced the amount of MDA, a key indicator of ROS, in the current investigation, especially at higher doses (4 mg/kg) (Faghihi & Mohammadi, 2017). According to earlier research, ROS can cause calcium-dependent depolarization of ATP and mitochondrial membrane potential decrease, which might increase status epilepticus processes (Carteri et al. 2019). Since pitavastatin antioxidant benefits in a variety of brain pathologies have been shown, it is believed that pitavastatin has potent antioxidant effects that confer anticonvulsive and antiepileptic properties (Musumeci, Bonaccorso, and Puglisi 2019).

MATERIAL AND METHODS

Preparation of animals

At the University of Kufa, the Faculty of Science provided 28 male Sprague Dawley rats, each rat weighing about 150-240 g and maturing at 10-12

weeks. The rats were housed in the Kufa College of Science's animal house. They were housed with humidity in a separate group caging system and temperature controls set to 24±2 C°. The animal cages were given water and a traditional chow meal based on their feed consumption. Medication was given to the animals to help them recover from the anxiety brought on by their environment changing, and they were separated for two weeks.

Study design

28 male rats, weighing between 150 and 240 grams at three months old, were split at random into four groups (seven rats: control group : Rats were fed a natural diet and were given water throughout the entire investigation; Group DMSO: For two weeks, rats were given 10 ml/kg/day of DMSO, a vehicle for pitavastatin, orally. For the doxorubicin Group (Cardiotoxicity Induction), for two weeks, 2.5 milligrams per kilogram was given intraperitoneally three times per week, for a total dose of 15 milligrams per kilogram (Moutabian et al. 2022). pitavastatin group rats were given pitavastatin by oral route in a dose 0.64 milligrams per kilogram per day along two weeks (Malik et al. 2011). (Malik et al., 2011).

Serum and tissue homogenate preparation

The body weight of each animal was measured 48 hours after the previous anticancer medication administration. Ketamine at 100 mg per kg and xylazine at 10 mg per kg were used to sedate the animals, both given intravenously. Following the administration of general anesthesia, the incision site was cut, the blood was drawn from the left ventricle of the heart through a heart perforation through a thoracoabdominal incision. In tubes containing clot activator gel, the blood samples were next put. The serum was then separated from the blood by centrifuging it at 4000 rpm for 10 minutes. Then the serum was used in an ELISA test with IL-1β and TNF-α testing kits that are readily available in the market.

Using a 1:10 (w/v) 0.1 M phosphate buffer saline and an ultrasonic liquid processor, the basal side of the heart was equilibrated (pH 7.4) after being washed removing any clots or red blood cells with ice-cold saline and then placed in a deep freeze (-80 °C) (Quagliariello et al. 2021). The supernatants were collected, homogenized, and centrifuged at 14000 rpm for 10 minutes at 4 degrees Celsius in accordance with the manufacturer's instructions to measure caspase-3, MDA, TAC, and Bcl-2 (PARS Bio chem, China).

Tissue sampling for histopathology

The epithelial portion was preserved, 5 M-thick pieces that have been embedded in a paraffin block and fixed in 10% neutral formalin using a microtome for histological analyses. Hematoxylin and eosin-stained tissue slices were examined under light microscopy (Hamidian et al. 2018).

Study parameter measurement

The manufacturer's instructions were followed when using ELISA kits to measure the concentrations of IL-1β, TNF-α, casp-3, Bcl-2, TAC, and MDA.

Statistical Analysis

By using Prism 8 for the analysis. The data have been displayed as mean plus standard error of the mean (SEM). To compare all groups against one another, we used one-way ANOVA. To compare histopathology changes in various groups, one-way ANOVA was used first, then post hoc analysis using the Bonferroni test with multiple comparisons $P< 0.05$ was set as the a level at which each test is statistically significant.

RESULTS

The dosage of doxorubicin used was 2.5 mg per kg, which led to cardiotoxicity. When compared to the DMSO group, the doxorubicin group showed TNF-α, MDA, IL-1β, and caspase-3 levels were higher, whereas Bcl-2 and TAC levels were lower. Pitavastatin considerably decreased inflammation associated with doxorubicin-induced cardiotoxicity ($P<0.05$), as shown by a reduction in the inflammatory biomarkers TNF-α and IL-1β (Figure 1 and

Figure 2). Treating rats with pitavastatin significantly lowered cardiac MDA levels (Figure 3) and increased cardiac TCA levels (Figure 4) when compared with induced group. Additionally, when compared to the group receiving only doxorubicin, pitavastatin inhibited doxorubicin-induced apoptosis by lowering cardiac caspase-3 levels. (Figure 5) and an important rise in Bcl-2 (Figure 6). Pitavastatin markedly improved the score differences between the doxorubicin group and treated group in the cardiomyopathy histological lesions (Figure 7).

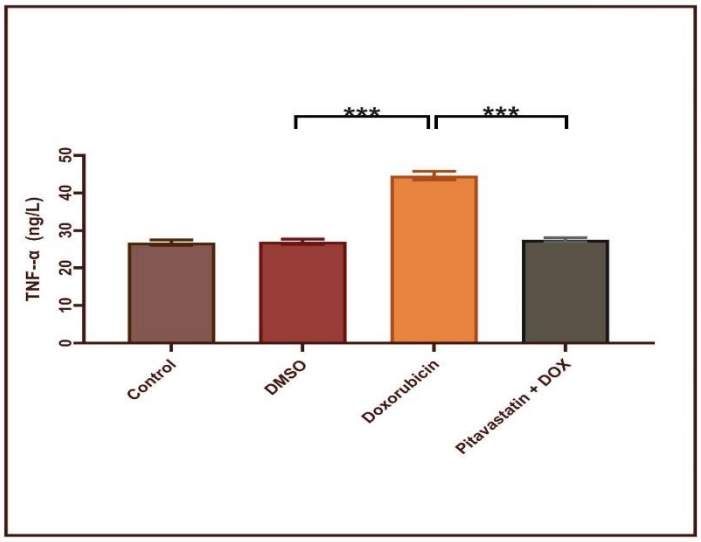

FIGURE 1: Serum TNF-α level of experimental groups. Rats received either DMSO (vehicle), Doxorubicin at a dose of 2.5 milligrams per kilogram, Doxorubicin at a dose of 2.5 milligrams per kilogram plus pitavastatin at a dose of 0.64 milligrams per kilogram, or left without receiving any treatment (control). Using a TNF-α ELISA kit, the serum TNF-α was measured. The data are displayed as mean±SEM. The Bonferroni multiple comparison test was used with a one-way ANOVA. *** P<0.001

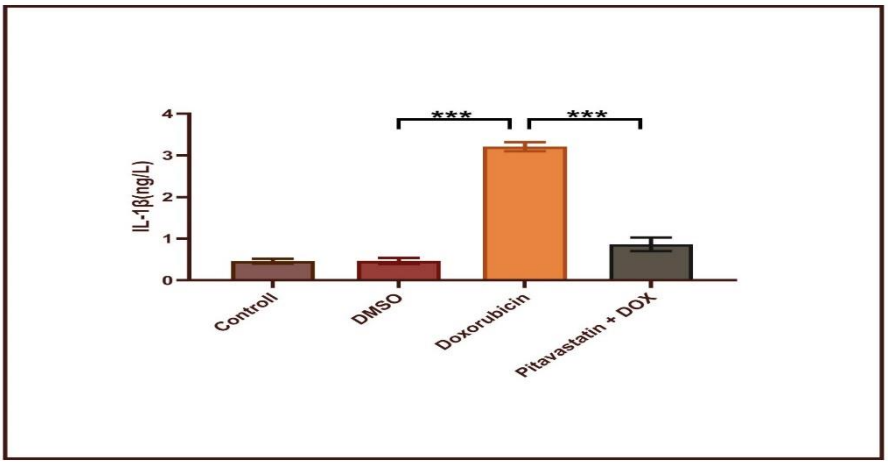

FIGURE 2: Serum IL-1β level of experimental groups. Rats received either DMSO (vehicle), Doxorubicin at a dose of 2.5 milligrams per kilogram, Doxorubicin at a dose of 2.5 milligrams per kilogram plus pitavastatin at a dose of 0.64 milligrams per kilogram, or left without receiving any treatment (control). Using an IL-1β ELISA kit, the serum IL-1β level was calculated. The data are displayed as mean±SEM. The Bonferroni multiple comparison test was used with a one-way ANOVA. ***P<0.001

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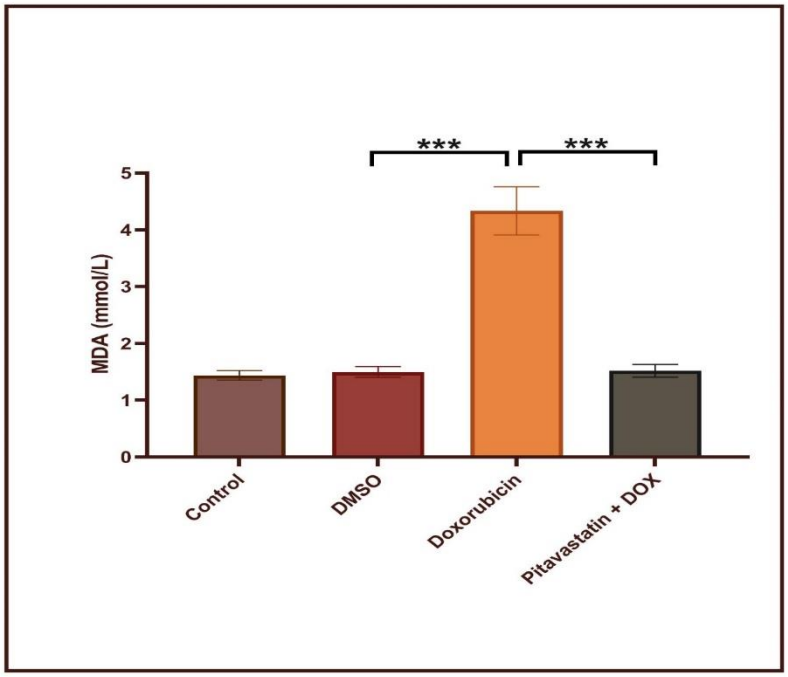

FIGURE 3: Cardiac MDA level of experimental groups. Rats received either DMSO (vehicle), Doxorubicin at a dose of 2.5 milligrams per kilogram, Doxorubicin at a dose of 2.5 milligrams per kilogram plus pitavastatin at a dose of 0.64 milligrams per kilogram, or left without receiving any treatment (control). The MDA ELISA kit was used to determine the cardiac MDA concentration. The data are displayed as mean ±SEM. The Bonferroni multiple comparison test was used with a one-way ANOVA. ***P<0.001

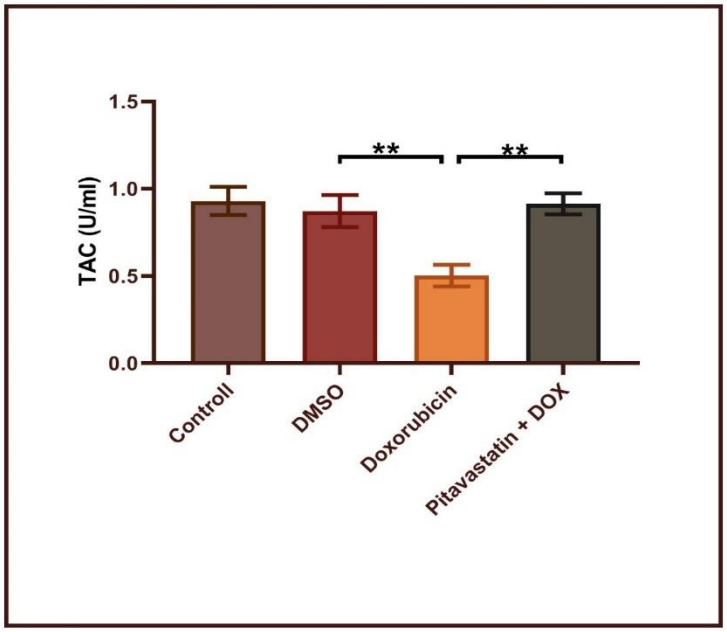

FIGURE 4: Cardiac TAC levels of experimental groups. . Rats received either DMSO (vehicle), Doxorubicin at a dose of 2.5 milligrams per kilogram, Doxorubicin at a dose of 2.5 milligrams per kilogram plus pitavastatin at a dose of 0.64 milligrams per kilogram, or left without receiving any treatment (control). Using the TAC ELISA kit, the cardiac TAC concentration was calculated. The data are displayed as mean± SEM. The Bonferroni multiple comparison test was used with a one-way ANOVA. ***P<0.01

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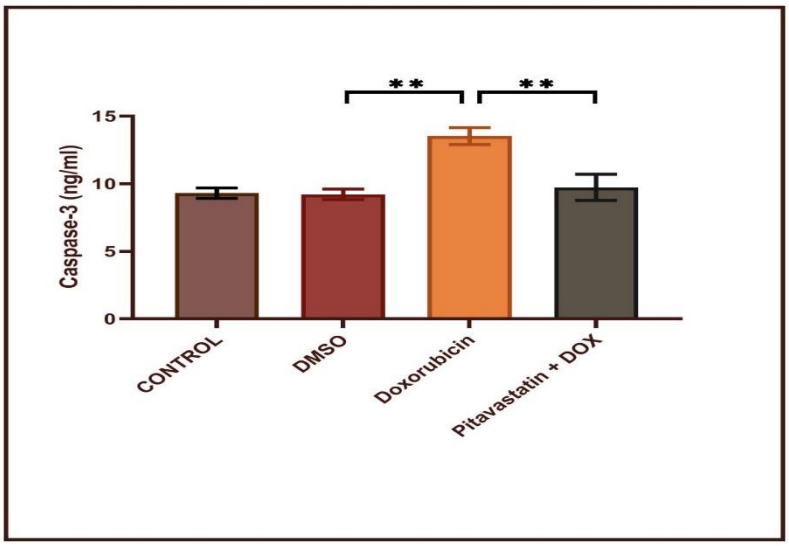

FIGURE 5: Cardiac caspase-3 level of experimental groups. Rats received either DMSO (vehicle), Doxorubicin at a dose of 2.5 milligrams per kilogram, Doxorubicin at a dose of 2.5 milligrams per kilogram plus pitavastatin at a dose of 0.64 milligrams per kilogram, or left without receiving any treatment (control). Using the caspase-3 ELISA kit, the cardiac caspase-3 concentration was calculated. The data are displayed as mean± SEM. The Bonferroni multiple comparison test was used with a one-way ANOVA. **P<0.01

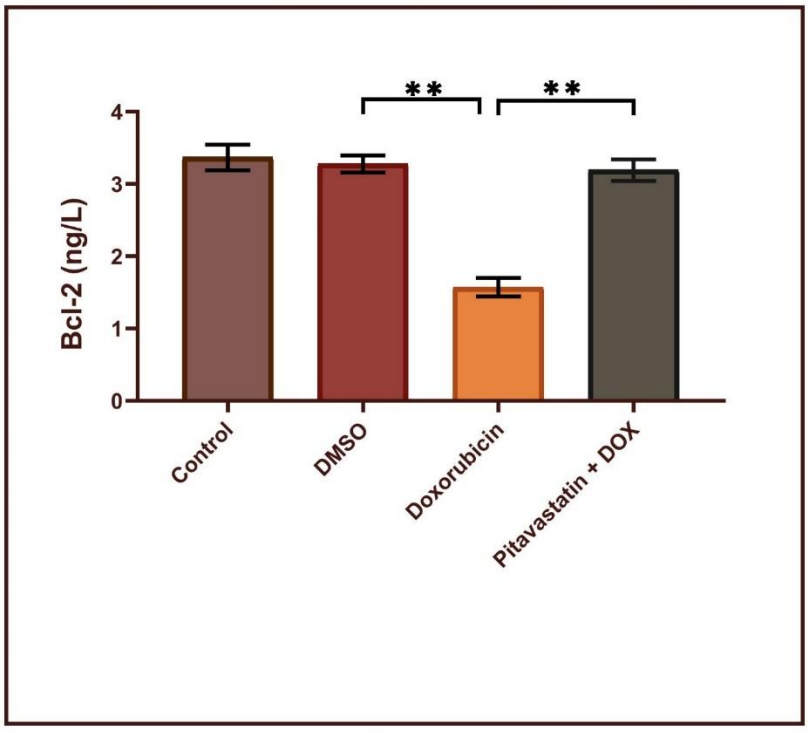

FIGURE 6: Cardiac Bcl-2 level of experimental groups. Rats received either DMSO (vehicle), Doxorubicin at a dose of 2.5 milligrams per kilogram, Doxorubicin at a dose of 2.5 milligrams per kilogram plus pitavastatin at a dose of 0.64 milligrams per kilogram, or left without receiving any treatment (control). The cardiac Bcl-2 concentration was calculated using the Bcl-2 ELISA kit. The data are displayed as mean ±SEM. The Bonferroni multiple comparison test was used with a one-way ANOVA. **P<0.01

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TABLE 1: Mean histopathological score and comparison between experimental groups.

Group	SEM±Mean	Comparison	P-Value
Control	0 ± 0	Control vs. DMSO	0.9702
DMSO	0 ± 0	DMSO vs. pitavastatin	0.9741
Doxorubicin	3.77 ± 0.182	Doxorubicin vs. DMSO	<0.0001
Pitavastatin	0.23 ± 0.16	Doxorubicin vs. pitavastatin	<0.0001

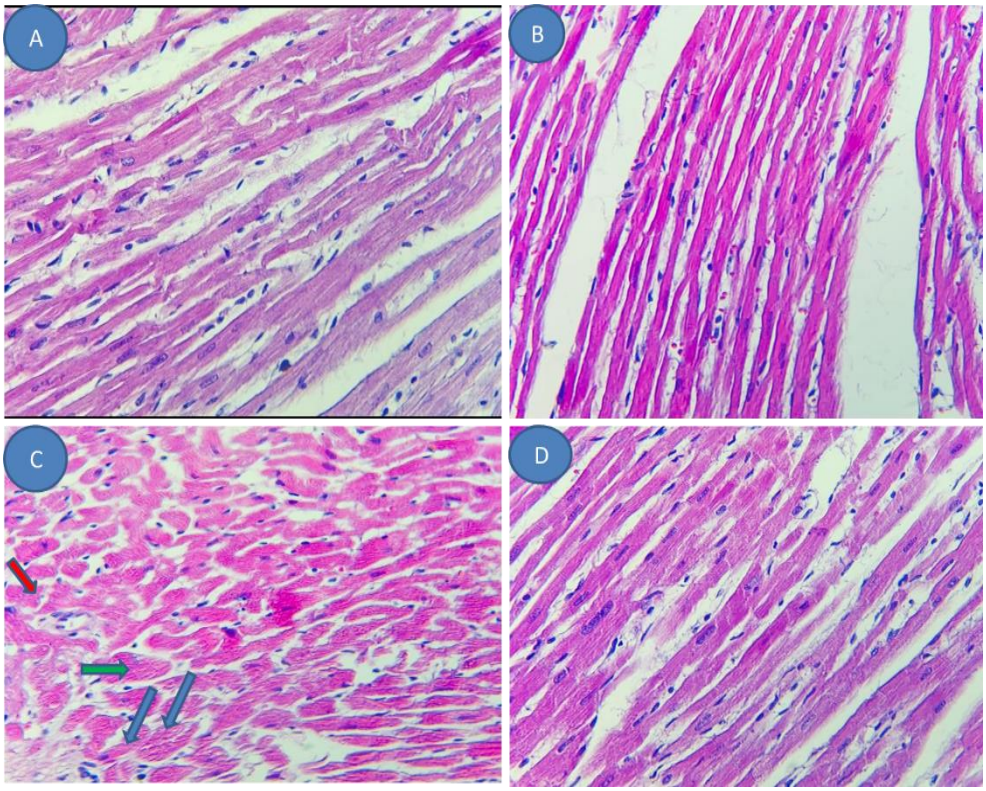

FIGURE 7: A- shows the control group cardiac muscle normal histology demonstrates that the appearance is damage-free. H&E. B- the vehicle group (DMSO) myocardium the absence of damage in the appearance shows normal histology. H&E. C- In a doxorubicin-treated rat, the myocardium displayed severe histopathological damage that was characterized by disorganized myocardial fibrils, stromal edema, necrosis, pyknotic nuclei (red arrow), perinuclear halo (green arrow), and fading of nuclei (blue arrow), H & E. D- Doxorubicin (2.5 milligrams per kilogram) and pitavastatin (0.64 milligrams per kilogram)-treated rats myocardiums exhibited normal histology, arranged myocardial fibrils, and staining H&E with no signs of damage.

DISCUSSION

Strong anti-tumor medication doxorubicin can be used by itself or in combination with other drugs to completely eradicate cancer (Li et al. 2019). New approaches been investigated to lessen or prevent doxorubicin-induced cardiotoxicity while preserving the drug's capacity to kill cancer cells. However, no clinically useful preventative medication has yet to be created (Russo et al. 2019). Numerous cardiac diseases have been linked to the onset and progression of IL-1β and TNF-α, inflammatory cytokines with negative inotropic effects and detrimental effects on left ventricular remodeling (Hanna and Frangogiannis 2020). DOX activates NF-B and increases the producing a number of pro-inflammatory cytokines, such as TNF-α, leading to a series of inflammatory events in the myocardium (Soltani Hekmat et al. 2021). The cause of doxorubicin-induced cardiomyopathy

was found to be a progressive rise in pro-inflammatory cytokines in heart tissue (Zhang et al. 2019). Cardiac inflammatory markers upregulated in the doxorubicin group over the control group confirms the inflammatory process linked to doxorubicin-induced cardiotoxicity, based on the findings of the present study. Additionally, these findings are in line with those of other investigations (Alyasiry et al., 2022; Aziz et al., 2020; Eid et al., 2021). Lower IL-1β and TNF-α levels in the pitavastatin-doxorubicin treated group when compared to the DOX group served as proof of this. In vivo studies that discovered neuroprotective effects connected to statin-induced reduced neuroinflammation support these findings. Reduced expression and/or release of neuroinflammatory mediators, such as TNF-α, IL-1β, and other mediators known to cause neuronal injury and reactive species that are oxidizing and nitrosating, is associated with the majority of reported protective effects (McFarland et al. 2018). Previous study revealed that A number of statins, including atorvastatin, fluvastatin, pitavastatin, rosuvastatin, and simvastatin, decreased the rise in inflammatory mediators (PGE2, TNF-α, and IL-1β) brought on by LPS. It is well established and documented that oxidative stress plays a crucial role in DOX-induced cardiotoxicity. Consequently, one of the goals of the current study is to assess Pitavastatin's capacity as an antioxidant in DOX-treated rats. According to this study, rats treated with pitavastatin and DOX as opposed to those treated with DOX alone showed reduced lipid peroxidation and preserved the antioxidant status of the heart tissue, as shown by a drop in MDA levels and an increase in TAC levels. Yate this is the first study to assess the impact of pitavastatin on levels of MDA and TAC in DOX cardiotoxicity, and it is consistent with earlier research that found MDA levels to be significantly higher than expected compared to the controls, but following statins treatment, MDA levels were lower, in terms of disease activity of Alzheimer and Parkinson's disease (Madeswaran, 2017). In this research Pitavastatin was found to have strong antiapoptotic properties, which may be the main mechanism underlying its cardioprotective abilities. This was demonstrated in this study that pitavastatin inhibited the apoptotic marker caspase-3 enzyme while increasing the anti-apoptotic marker Bcl-2 in rats when compared to the DOX-induced untreated group, indicating that Pitavastatin provides protection against the cardiotoxicity brought on by DOX. These findings come in agreement with previous studies such as (Xian et al. 2017) and (Chen et al. 2020) which demonstrated that pitavastatin safely increases the efficacy of cisplatin in lung cancer cells as well as in a tumor xenograft model; Inhibition of the Ras/Raf/MEK and PI3K/Akt/mTOR signaling pathways mediates this effect. The present study's histopathological findings demonstrated that pitavastatin when compared to the DOX group, there was a significant improvement in the CMY severity score, indicating that pitavastatin had the ability to lessen the lesions of cardiac tissue caused by DOX. Pitavastatin cardio-protective effects have also been demonstrated by earlier study that investigated that pitavastatin lowers reducing the production of free radicals to reduce collagen deposition and inflammation in isoproterenol-induced cardiomyopathy (Iqbal et al. 2019). Pitavastatin suppressed the inflammatory response in the myocardium, as demonstrated by lower levels of Tnf-alpha and Interleukins, and also inhibited the final stage of apoptosis, according to the findings of this study. It also interfered with the oxidative pathway, as demonstrated by lower levels of lipid peroxidation and preserved cardiac antioxidant status, as shown by higher levels of Bcl-2 and lower levels of caspase-3 in cardiac tissue. All of these findings may offer a mechanistic explanation for pitavastatin cardio-protective effect in DOX-induced cardiomyopathy.

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