

Histopathological Evaluation of the Cardioprotective Effects of Ten Medicinal Plants in a Rat Model of Isoproterenol-Induced Heart Failure

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Article

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Abstract

Introduction:

Heart failure (HF) is a leading cause of mortality worldwide, often characterized by pathological myocardial remodeling and fibrosis. While we previously reported the therapeutic benefits of ten medicinal plants on echocardiographic and serum biomarkers in isoproterenol (ISO)-induced HF rats, their effects on cardiac histopathology remained unexplored. This study aimed to perform a detailed histopathological evaluation to determine the tissue-level protective effects of these plants.

Methods

For this histopathological evaluation, cardiac tissue samples were sourced from our previously established HF model. In that model, rats received intraperitoneal pretreatments with the respective plant extracts for 30 days prior to ISO induction. Following the experimental period, heart sections were prepared, stained with Hematoxylin and Eosin (H&E), and then examined microscopically by an observer who was blinded to the group assignments. The extent of pathological changes—specifically fibrosis, inflammation, vacuolization, necrosis, and hypertrophy—was systematically quantified using a standardized 0–5 scoring scale.

Results

ISO administration induced significant histopathological damage (median scores of 2 + to 3 + across all parameters). Pretreatment with all plant extracts significantly reduced these scores compared to the ISO-only group (* $p < 0.001$). *Centella asiatica* exhibited the most potent protective effect, showing near-normal cardiac architecture with only mild myocyte hypertrophy (score 1+). Extracts of *Allium sativum*, *Berberis vulgaris*, and *Peganum harmala* also showed strong attenuation of histopathological damage. Notably, all extracts except *Apium graveolens* completely prevented ISO-induced fibrosis.

Conclusion

The findings demonstrate that these medicinal plants, particularly *Centella asiatica*, confer significant cardioprotection by preserving cardiac tissue architecture in ISO-induced HF. This provides a crucial histopathological correlate to our previous functional findings and supports their potential as adjunctive therapeutic agents for heart failure.

Introduction

Cardiovascular disorders are correlated to the abnormal function of the heart such as heart failure, sudden cardiac events, cerebrovascular events etc [1]. They may lead to high burden of morbidity and

mortality in different countries specially developing countries [2]. Ischemic injury leads to the development of myocardial fibrosis due to the negligible regenerative capacity of the heart. Myocardial fibrosis is associated with increased deposition of matrix proteins in the myocardium. Myocardial fibrosis can be divided into “reactive interstitial” and “reparative” subtypes [3]. Reactive interstitial fibrosis is characterized by expansion of the myocardial interstitial space without significant loss of cardiomyocytes. Reparative fibrosis involves collagen deposition in response to myocardial ischemia. The adaptive responses to preserve cardiac output are reactive interstitial fibrosis and cardiomyocyte hypertrophy. Eventually, cardiomyocytes undergoing necrosis and apoptosis cause reparative fibrosis [4]. Myocardial fibrosis plays an important part in the pathogenesis of ischemic cardiomyopathy, which contributes to systolic and diastolic dysfunction. Ischemic injury to the heart leads to myocardial fibrosis, and the end result is heart failure [3].

It is well recognized that free radicals generated in ischemic tissues causes metabolic stresses which results in degradation of tissue defense system, leading to myocardial damage and necrosis [5]. During the years, many attempts have been performed to develop non-toxic and relatively safe antioxidants from natural products to decrease the heart injury during ischemia and/or to develop preventive agents. Medicinal plants, plants based foods and their compounds have received great attention for their salutary effects and potential to treat many aspects of ischemic heart disease or myocardial infarction [6, 7]. In parallel, the use of herbs in pharmacotherapy is also rising along with a realization that herbal products can influence the course of heart diseases and may provide an integrated approach of nutritional substances, which helps in restoring and maintaining, the balanced body systems [8]. We evaluated previously the effects of ten medicinal plants on isoproterenol-induced heart failure in rats and reported positive echocardiographic and laboratory outcomes [9]. However, the underlying effects on cardiac tissue histology remained uncharacterized. Therefore, the present study was designed to specifically evaluate the histopathological changes in the heart to provide a morphological correlate for the functional improvements and to further elucidate the cardioprotective mechanisms of these medicinal plants.

Materials and Methods

This histopathological analysis utilizes cardiac tissue samples collected from a previously reported experimental study on heart failure [9]. The primary echocardiographic and serum biomarker data from that study have been published, while the detailed histopathological findings are presented here for the first time. The experiment was performed in the animal laboratory of the medical school, Mashhad University of Medical Sciences, Mashhad, Iran.

Chemicals

ISO (Isoproterenol hydrochloride, Product Number: I-5627) was purchased from Sigma-Aldric Company (St Louis, MO, USA). Ketamine was purchased from Pharma Company (Warburg, Germany).

Extract preparation

Plants extraction was conducted by the previously reported investigation. In summary, Berberis integerrima and Berberis vulgaris fruit, Apium graveolens and Peganum harmala seeds, Citrus aurantium bulb, Citrus aurantifolia peel, Cerasus avium stalk and Garlic (Allium sativum) bulbs, Centella asiatica and Curcuma longa were purchased from a university drugstore and approved by a pharmacognosist. Specific extraction was performed for each of the plants, as described before [9]. All of extracts were used intraperitoneal (IP) according to previous published studies. Treatment protocol in different groups is summarized in the below table.

Table 1
Treatment Groups and Protocol

Group Number	Group Name	Treatment Description
1	Sham	Normal saline
2	ISO	Isoproterenol (10 mg/kg, 7 days)
3	Citrus aurantifolia + ISO	Extract + ISO
4	Centella asiatica + ISO	Extract + ISO
5	Curcuma longa + ISO	Extract + ISO
6	Allium sativum + ISO	Extract + ISO
7	Apium graveolens + ISO	Extract + ISO
8	Citrus aurantium + ISO	Extract + ISO
9	Peganum harmala + ISO	Extract + ISO
10	Berberis vulgaris + ISO	Extract + ISO
11	Berberis integerrima + ISO	Extract + ISO
12	Cerasus avium + ISO	Extract + ISO

**Note: n = 8 per group. Specific extract doses were administered intraperitoneally for 30 days, as detailed in [9].*

Animal and heart failure model induction

We used male Wistar rats (16 weeks old). The animals were housed in the animal laboratory of the medical faculty under standard conditions. The animal house was maintained at a temperature of 25 ± 2°C with relative humidity 50 ± 15% and a 12 h dark/light cycle. Rats were kept under standard conditions and received food and water ad libitum. All animal experiments were undertaken with the approval of Institutional Animal Ethics Committee of Mashhad University of Medical Sciences. Ninety-six male rats

with a weight range of 180–250 g (Mean 203.37 ± 20.15 g) were randomly allocated into twelve groups (n = 8 each) as defined in Table 1. ISO was injected subcutaneously (10 mg/kg) in rats for 7 days to induce heart failure.

Histopathological examination

Hearts were removed, freed of connective tissue, washed extensively with saline to remove all contaminating blood, and weighed. The received heart samples were placed in 10% formaldehyde solution for fixation. Specimens were embedded in paraffin and then cut into 5 µm thick sections. After staining with Haematoxylin and Eosin (H & E) according to the manufacturer's instructions, sections were examined by an experienced observer blinded to the treatment protocol using a microscope (Olympus, Tokyo, Japan). Ten fields were selected randomly from five sections in each heart and the images of myocardial sections were stored. The parameters of pathological changes observed were tabulated and graded using a scale of 0–5 as defined below [10]:

Score	Definition
0	Parameter not present
1+	Parameter present in up to 25% of area examined
2+	Parameter present in between 26% to 50% of area examined
3+	Parameter present in between 51% to 75% of area examined
4+	Parameter present in more than 75% of area examined
5+	Parameter present in more than 90% of area examined

Parameters assessed: Fibrosis, Myocyte inflammation (based on enlargement and internalization of nuclei), Myocyte vacuolization, Necrosis Degeneration, Myocyte hypertrophy.

Ethics

This study was approved by the ethical committee of Mashhad University of Medical Sciences, Mashhad, Iran (approval code: IR.mums.sp.1396.120). All procedures were conducted in accordance with the Helsinki ethical declaration. All interventional procedures in rats were performed under anesthesia.

Statistics

Data were presented as mean $\pm$ SD for laboratory data and median for histopathological scores. One-way analysis of variance (ANOVA) was applied for statistical analysis of laboratory data, followed by post-hoc analysis. The Kruskal-Wallis test was used for the analysis of histopathological scores. A *p*-value of less than 0.05 was considered significant.

Results

Gross pathology

The hearts of the ISO-treated rats were larger and congested, without signs of necrosis throughout the musculature. The hearts of the rats in other groups (*Apium graveolens* + ISO, *Citrus aurantium* + ISO, *Berberis vulgaris* + ISO, *Berberis integerrima* + ISO and *Cerasus avium* + ISO) were also large in size with no signs of gross necrosis. It was shown that the size of the hearts in all treatment groups was significantly lesser than in the ISO group. However, the HW/BW ratio was different in some groups (Fig. 1).

Laboratory findings

Table 2 shows the changes of some biochemistry laboratory indices.

Table 2
Changes in the levels of CPK, LDH, CKMB and Hcy in different groups

Groups (n = 8)	LDH	CPK	CKMB	Hcy
Sham	587.50 ± 343.52##	2986.12 ± 1968.58##	33.02 ± 220.56##	4.60 ± 1.10##
ISO	1616.62 ± 560.17	9876.25 ± 5660.13	1293.98 ± 279.06	14.01 ± 3.33
Citrus aurantifolia + ISO	1190.25 ± 323.87#	349.75 ± 71.72##	332.07 ± 99.94##	8.66 ± 0.66##
Centella asiatica + ISO	1863.50 ± 121.99	2412.37 ± 1016.63##	660.38 ± 95.04##	6.05 ± 0.51##
Curcuma longa + ISO	1526.32 ± 438.87	1759.37 ± 830.59##	964.42 ± 278.44##	8.05 ± 0.83##
Allium sativum + ISO	801.50 ± 648.42##	592.50 ± 687.82##	241.03 ± 187.62##	5.71 ± 0.35##
Apium graveolens + ISO	985.12 ± 736.41##	1491.87 ± 433.61##	274.60 ± 170.44##	5.23 ± 0.07##
Citrus aurantium + ISO	1384.62 ± 315.61	4478.87 ± 1685.99##	978.52 ± 318.89##	7.18 ± 0.76##
Peganum harmala + ISO	1563.12 ± 212.10	288.19 ± 16.38##	404.67 ± 32.40##	9.17 ± 0.31##
Berberis vulgaris + ISO	1283.25 ± 473.43	229.12 ± 42.52##	399.40 ± 193.93##	7.36 ± 0.50##
Berberis integerrima + ISO	1311.25 ± 115.34	1232.87 ± 2194.30##	252.88 ± 27.59##	8.36 ± 0.76##
Cerasus avium + ISO	1383.25 ± 278.50	3326.87 ± 2121.80##	987.83 ± 290.54##	7.98 ± 1.19##

CPK= Creatine phosphokinase; LDH= lactate dehydrogenase; CKMB= Creatine kinase-MB; Hcy= homocysteine; Compared with CHF model group: #p < 0.05, ##P < 0.01.

It is shown that Citrus aurantifolia, Allium sativum and Apium graveolens groups significantly decrease the LDH level in comparison with model group. CPK, CKMB and Hcy in all groups were markedly better than model group (P < 0.05). Centella asiatica, Allium sativum and Apium graveolens had the best results for Hcy, Apium graveolens, Berberis integerrima and Allium sativum for CKMB, Citrus aurantifolia, Peganum harmala and Berberis vulgaris for CPK and Citrus aurantifolia, Allium sativum and Apium graveolens for LDH.

Histopathological findings

Table 3 summarizes the observed pathological changes in the samples of the different groups, in relation to the type of change observed and the extent of spread of each type of pathological change.

Table 3
Median of pathological score in different groups

Groups (n = 8)	Myocyte vacuolization	inflammation	Myocyte hypertrophy	Necrosis degeneration	fibrosis
Sham	0	0	0	0	0
ISO	3+	3+	2+	2+	2+
Citrus aurantium + ISO	1+	1+	1+	1+	0
Centella asiatica + ISO	0	0	1+	0	0
Cerasus avium + ISO	1+	2+	0	1+	0
Peganum harmala + ISO	1+	1+	0	1+	0
Allium sativum + ISO	0	1+	1+	1+	0
Berberis vulgaris + ISO	0	1+	1+	1+	0
Berberis integerrima + ISO	0	1+	1+	1+	0
Curcuma longa + ISO	0	0	1+	1+	0
Apium graveolens + ISO	0	1+	1+	1+	1+
Citrus aurantifolia + ISO	0	1+	1+	1+	0

The Kruskal Wallis Test illustrated that changes in each parameter of pathological examination were significantly lower in all treatment groups compared to the model group (*p*<0.001). Except for the Apium graveolens group, all other groups completely prevented the development of fibrosis related to model induction. The most potent effect was observed in the Centella asiatica group, which showed only mild myocyte hypertrophy (1+). Figure 2 demonstrates the effects of pretreatment on histopathological changes in representative groups.

Discussion

The present investigation offers the first comprehensive histopathological evidence detailing the cardioprotective actions of ten medicinal plants in a rat model of ISO-evoked HF. Our data demonstrate that although all tested extracts provided considerable tissue-level protection, *Centella asiatica* was preeminent in maintaining normal cardiac architecture. These morphological findings establish a critical tissue-based correlate for the functional and biochemical enhancements we reported previously [9]. In that earlier study, we found that *Allium sativum*, *Peganum harmala*, and *Berberis vulgaris* could significantly enhance cardiac performance by attenuating left ventricular remodeling and reducing levels of hs-CRP and Pro-BNP.

The histopathological data from the current study are in strong concordance with these prior observations. For instance, groups pretreated with *Allium sativum* and *Berberis vulgaris* displayed noticeably diminished scores for inflammation, vacuolization, and necrosis. The superior outcome observed with *Centella asiatica* highlights its well-documented robust antioxidant and anti-fibrotic capabilities, a finding that corroborates previous reports [11]. Conversely, the mild fibrosis still present in the *Apium graveolens* group, despite favorable serum biomarker profiles, suggests that its primary protective mechanism might be more reliant on systemic anti-inflammatory pathways rather than exerting a direct anti-fibrotic influence at the myocardial tissue level in this specific model.

The underlying mechanisms of ISO-induced damage, including cytosolic Ca^{2+} overload and excessive free radical production [12, 13], are effectively countered by the antioxidant constituents of these plants. For instance, the berberine in *Berberis vulgaris* has been shown to antagonize ISO-induced myocardial damage and arrhythmias [14, 15], a finding consistent with our histological evidence of reduced necrosis. Similarly, the organosulfur compounds in *Allium sativum* are known to activate mitochondrial biogenesis and reduce hypertrophy [16], which aligns with our observation of improved myofibril arrangement and reduced hypertrophy.

The significant reduction in serum levels of CPK, LDH, and CK-MB in most treatment groups confirms the attenuation of cardiomyocyte membrane damage and necrosis [17, 18]. The concordance between the improved serum biomarker profiles and the favorable histopathological scores strengthens the validity of our conclusion that these plants offer genuine cardioprotection.

This experimental study showed the protective effect of different potential natural products' extracts against CHF induced by ISO in rats. In addition, this rat model revealed the relationships between laboratory measurements in blood and histological changes in the heart tissue. In the first part of our previous published of this project, we showed some laboratory indices and echocardiographic benefits of some of these medicinal plants. We showed that *Allium sativum*, *Peganum harmala* and *Berberis vulgaris* could significantly improve cardiac function by improvement of left ventricular remodeling, lowering hs-CRP and Pro-BNP and echocardiographic indexes without liver or renal side effects [9]. In this study, we illustrated that all groups had protective effect in pathological features of the heart tissue. However, *Centella asiatica* had the best protective effect and *Allium sativum*, *Apium graveolens*,

Peganum harmala and *Berberis vulgaris* had the best results in inflammatory laboratory results. These results were approximately adopted with echocardiographic findings.

The effects of ISO on heart are mediated through Beta1 and Beta2 receptors. Both of these receptors mediate the positive inotropic and chronotropic effects to beta receptor agonists [19]. Thus, ISO produces relative ischemia or hypoxia due to myocardial hyperactivity and coronary hypotension [20], and makes myocardial ischemia because of cytosolic Ca²⁺ overload [21]. Moreover, it induces myocardial ischemia because of excessive production of free radicals resulting from oxidative metabolism of catecholamines [22]. In line with our results, it was shown that hearts of rats pretreated by 100 mg/kg *Centella asiatica* extract had mild to moderate multifocal myocardial necrosis with mild to moderate infiltration of lymphocytes and macrophages [11]. We used this dose in our investigation. However, in mentioned study, higher dose (200 mg/kg) of *Centella asiatica* extract, exhibited mild necrosis and less infiltration of inflammatory cells that showed the heart sections to have similar histo-architecture to that of normal rats [11]. It can be due to antioxidant effect of its extract. *Berberis vulgaris* was one of the natural products with high protective effect on induction of CHF model in this study. It was shown that berberine, an active constituent of *Berberis vulgaris*, has an antagonistic effect on isoproterenol-induced myocardial damage and the ischemic arrhythmia caused by ligation of the anterior descending branch of the left coronary artery in rat models [23, 24]. In another study, the antagonistic effects of berberine on Chuan-wu-induced acute myocardial injury were observed in rats. The results revealed that berberine significantly reduced the degree of arrhythmia induced by Chuan-wu, and improved the survival rate of rats. Analysis of myocardial enzymes and histopathological examination demonstrated marked improvements in berberine pretreatment groups [25]. In this study, we used 50 mg/kg/day *Allium sativum* extract and it significantly lower the inflammatory markers beside mild affected histopathologic findings. In previous studies, it was demonstrated that this extract with higher dose had significant improving the regular arrangements of myofibrils and normal and central distribution of nuclei, even approximately similar to the normal individuals at the end of the study in pretreated MI rats [26]. Another study was confirmed our findings, too [16].

The serum levels of CPK, CK-MB and LDH are quantitative indicators of loss of membrane integrity during myocardial damage [17]. In the present study, in ISO treated rats there was an increase in the levels of the marker enzymes LDH and CK, CKMB in the serum. The plasma LDH and CK enzyme activities are important measures for both early and late phases of cardiac injury. The release of the cardiac specific iso-enzymes LDH1 and LDH2-into the circulation may be because of the necrosis induced by ISO [18]. These finding confirm the onset of myocardial necrosis and leaking out of the marker enzymes from heart to blood [27]. We illustrated that majority of natural products lead to decrease the level of LDH, CPK and CKMB significantly and prevent the cardiac injury.

Conclusion

In conclusion, the present study demonstrates that the tested medicinal plants reduce ISO-induced histopathological damage in a rat model of CHF. *Centella asiatica* emerged as the most effective in

preserving cardiac tissue structure, with *Allium sativum* and *Berberis vulgaris* also showing strong protective effects. These histopathological findings confirm and extend our previous echocardiographic and laboratory results, suggesting that a complex of such medicinal plants, particularly those identified as most potent, could be a promising novel supplementary therapeutic approach for heart failure.

Declarations

Ethics approval and consent to participate

This study was approved by Mashhad University of Medical Sciences ethical committee.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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Author Contribution

S.A.M. and F.K collected data and major contributor in writing the manuscript. A.S participated in animal works, wrote the first draft of the manuscript and final version. Sh.T.J. examined the samples and reviewed the last version. S.M. participated in performing animal works and reviewed and confirmed the last version. All authors read and approved the final manuscript.

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Data Availability

Data are however available from the authors upon reasonable request and with permission of the corresponding author.

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Figures

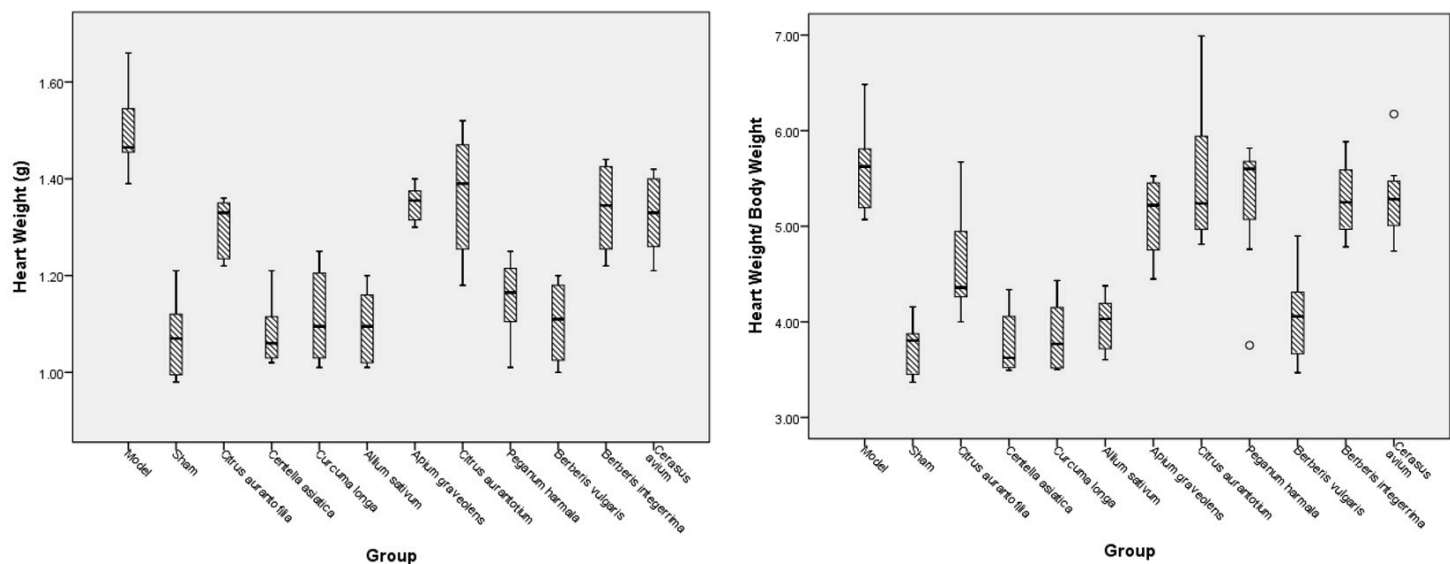


Figure 1

Effects of different natural products on body weight and heart weight in rats with CHF.

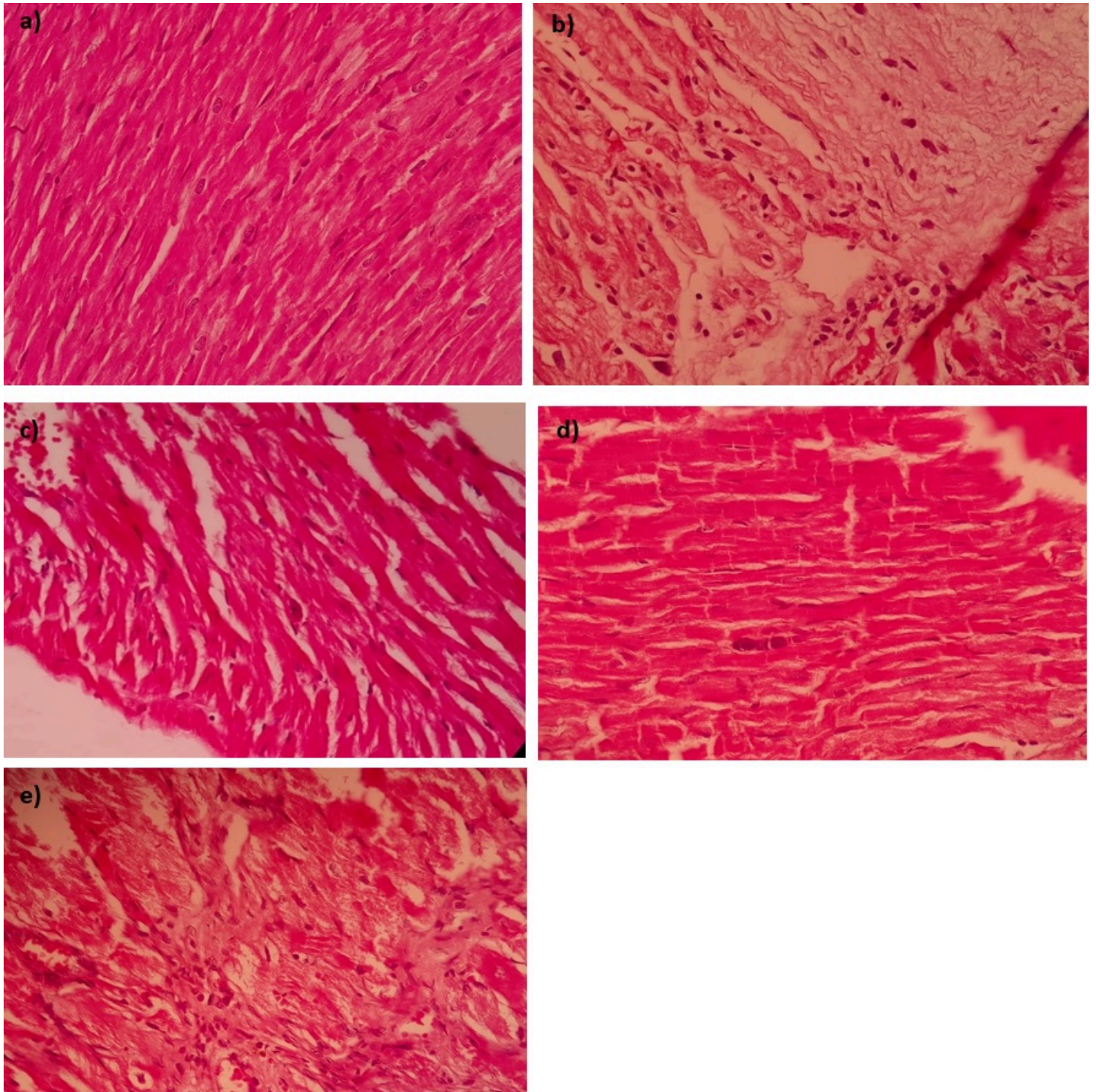


Figure 2

(a) normal control heart tissue demonstrating cardiomyocytes; (b) CHF isoproterenol-induced model (ISO) showed marked edema, inflammatory cell infiltration, fibrosis and necrosis; (c) Pretreatment with Peganum harmala + ISO showed minimum reduction of edema, inflammatory cell infiltration, and necrosis; (d) Allium sativum + ISO produced moderate reduction of edema, inflammatory cell infiltration, and necrosis; (e) Centella asiatica+ ISO produced maximum reduction of edema, inflammatory cell infiltration, and necrosis. (400X magnification)

