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Cardiotoxicity of hydroalcoholic extract of *Lepidium draba* in isoproterenol-induced heart failure in rats

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ABSTRACT: Considering that the general belief is that medicinal plants have less side effects, they are usually consumed without a prescription, so it is necessary to study the safety of these plants on different body systems including the cardiovascular system. The aim of the present study is to evaluate the effects of the hydroalcoholic extract of *L. draba*, one of the popular traditional medical plants, in isoproterenol-induced heart failure in rats. For induction of heart failure in rats a subcutaneous injection of isoproterenol (5 mg/kg/day for 10 days) was used. Hydroalcoholic extract of *L. draba* was injected intraperitoneally (ip) at doses of 50, 250 and 500 mg/kg for 10 days. Then, hemodynamic, electrocardiogram, and histopathological changes as well as lipid peroxidation and lactate dehydrogenase (LDH) levels were investigated. Our results showed that administration of *L. draba* extract increased myocyte necrosis and destruction as well as myocardial glycogen accumulation in comparison to HF (Iso) group. Treatment with *L. draba* extract significantly increased malondialdehyde and LDH levels in comparison to HF group ($P<0.01$ and $P<0.05$ respectively). Additionally, treatment with *L. draba* extract for ten days had no significant effect on hemodynamic parameters and electrocardiogram pattern. In conclusion, our results for the first time showed the cardiotoxic effects of *L. draba* in heart failure through the destruction of heart tissue, increase in glycogen accumulation, malondialdehyde and lactate dehydrogenase levels. Therefore, it is suggested that the patients suffering from heart failure should avoid long-term consumption of this plant.

KEYWORDS: *Lepidium draba*; Cardiotoxicity; Heart failure; Isoproterenol; Glycogen; Malondialdehyde

1. INTRODUCTION

Heart failure is a progressive fatal disease which occurs when the cardiac output does not meet the body's metabolic needs. Heart failure results in ventricular remodeling, ventricular hypertrophy and reduced ejection fraction [1]. Furthermore, oxidative stress and systemic inflammation are other effective factors involved in heart failure [2-4]. Oxidative stress is a condition in which the production of Reactive Oxygen Species (ROS) is much higher than the antioxidant defense, which plays an important role in the pathophysiology of heart failure [2]. If the amount of oxidative stress decreases or the amount of antioxidants increases, it will have a significant effect on heart failure and, of course, its complications. In the case of inflammation, increased blood circulation and proinflammatory cytokines are associated with chronic heart failure. Increased production of proinflammatory cytokines, including TNF-α, IL-6, IL-1, and IL-18, have direct effects on the structure and function of cardiomyocytes that also endanger surrounding tissue. Indeed, cardiomyocyte hypertrophy, contractile dysfunction, apoptosis and extracellular matrix remodeling greatly contribute to the progression of chronic heart failure [5] and minimizing these complications should be emphasized.

Unsupervised use of medicinal plants is one of the important risk factors that should be considered in human health especially in cardiovascular diseases. Many patients believe that medicinal plants are always safe and do not pose any risk to their health, while there are many reports on the toxic effects of medicinal plants that show severe complications in various diseases. *Brassicaceae* is a medicinal plants family with specific therapeutic effects. It has been reported that *Lepidium Sativum* and *Lepidium apetalum* from *Brassicaceae* family, demonstrates cardioprotective effects in heart failure [6, 7].

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Lepidium daraba (*L. draba*) is the other example of *Brassicaceae* family which is a perennial plant that can have anti-inflammatory and antibacterial effects due to its rosmarinic acid content. In addition, the presence of 4-hydroxybenzoic acid may indicate antibacterial, antifungal and estrogenic effects of this plant [8]. Although brassicaceous crops are now generally considered to be beneficial to human health, they can have side effects such as anti-nutritional activity, hemolytic anemia and adverse effects on thyroid metabolism. Most importantly, these plants due to their erucic acid cause abnormal accumulation of fat and myocardial damage [9]. The *Brassicaceae* vegetables are rich in glucosinolates and phytates, which have been found to have adverse effects on human and animal health. For instance, the glucosinolates and their by-products are toxic and contribute to the bitter, hot, and pungent flavors of these vegetables [10]. However, recent studies suggest that this family of medicinal plants has both positive and negative nutritional effects [11]. While they possess anticarcinogenic properties, they also exhibit distinct toxicological effects. Moreover, the impact of various glucosinolate degradation products on individual organisms is not uniform and often unknown. Excessive consumption of these compounds can be highly toxic [12]. Interestingly, as a member of the *Brassicaceae* family, the effects of *L. draba* on cardiovascular disorders, such as heart failure, remain unexplored. Therefore, this study was conducted to evaluate the potential effects of *L. draba* on isoproterenol-induced heart failure in rats.

2. RESULTS

2.1. Effects of hydroalcoholic extract of *L. draba* on heart rate and mean arterial pressure (MAP)

The results demonstrated that heart rate was reduced significantly in Iso group compared with control group (P<0.05) (Fig.1.A), but all three groups of treated rats with hydroalcoholic extract of *L.draba* didn't show any significant changes in heart rate. As the same of HR evaluation, mean arterial pressure was reduced significantly in the Iso group (P<0.05), but *L. draba* didn't improve MAP in treated groups (Fig.1.B).

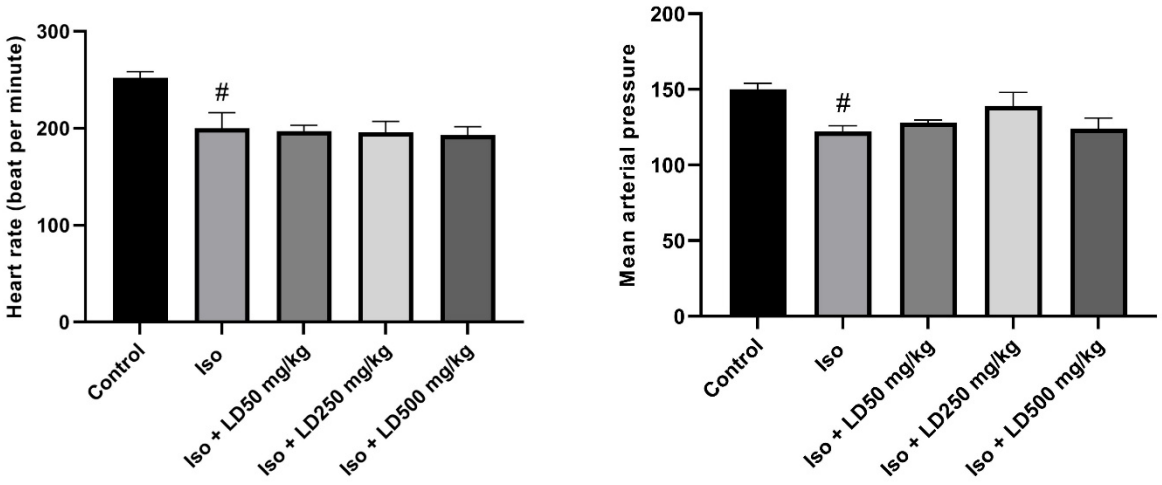

Figure 1. The effects of hydroalcoholic extract of *L. draba* at doses of 50, 250, and 500 mg/kg on heart rate (A) and mean arterial blood pressure (mmHg) (B) in isoproterenol-induced heart failure in rats. Iso: isoproterenol; LD: *L. draba*. Values are the mean ± S.E.M (n = 6); # P < 0.05 from respective control value using one-way ANOVA with Tukey post-hoc test.

2.2. Effects of hydroalcoholic extract of *L. draba* on electrocardiogram

Animals in control group showed normal pattern of electrocardiogram, whereas rats in Iso group showed significant decrease in R-amplitude (P<0.01) and ST segment depression (indication of myocardial ischemia) as compared to control group. Administration of *L. draba* hydroalcoholic extract did not improved ECG pattern and slightly increased R-amplitude (P<0.05) as compared with Iso group (Figure 2 and Table 1).

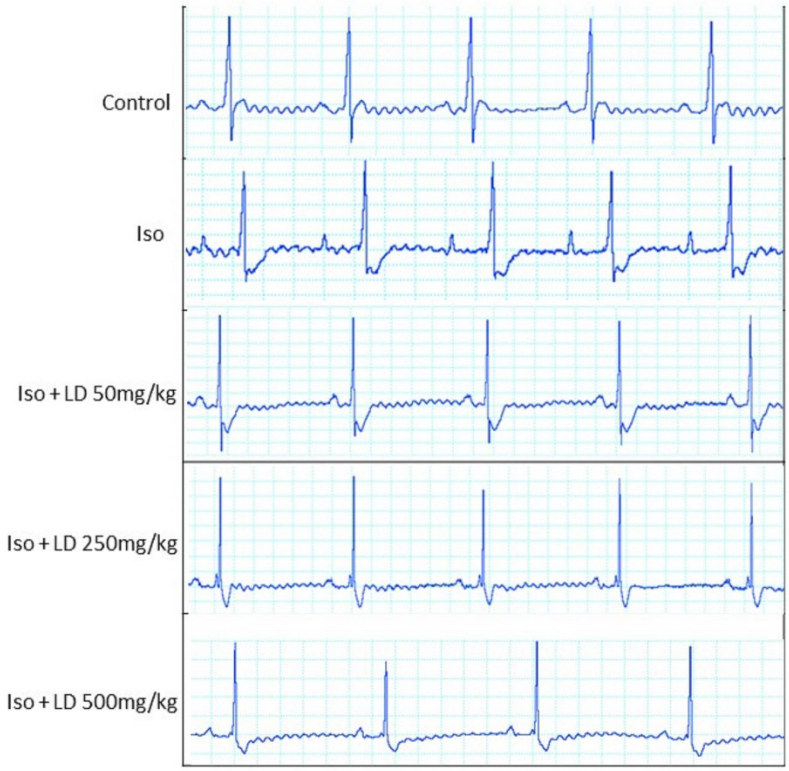

Figure 2. Representative ECG pattern and changes (recorded from limb lead II) in control, Iso, and *L. draba* extract treated groups.

Table. 1. Effects of *L. draba* on electrocardiographic parameters in isoproterenol-induced heart failure in rats

Groups n=6	PR interval (s)	P duration (s)	QRS complex (s)	R-R interval (s)	R-amplitude (mv)	ST Depression (mv)
Control	0.055±0.000	0.018±0.000	0.016±0.000	0.2±0.01	0.75±0.02	0.06±.002
Iso	O.061±0.002[a]	0.028±0.003[a]	0.02±0.005	0.27±0.03[a]	0.52±0.02[b]	0.2±0.08
Iso + LD50 mg/kg	0.054±0.000***	0.027±0.001	0.022±0.009	0.3±0.01	0.7±0.01*	0.28±0.08
Iso + LD250 mg/kg	0.055±0.000**	0.2±0.003	0.022±0.005	0.31±0.01	0.68±0.03*	0.1±0.03
Iso + LD500 mg/kg	0.06±0.001	0.031±0.003	0.028±0.006	0.3±0.01	0.56±0.03	0.12±0.02

Data are expressed as mean ± S.E.M. [a]P<0.05; [b]P<0.01 vs control group. * P<0.05; **P<0.01; ***P<0.001 as compared with isoproterenol treated group using one-way ANOVA with Tukey post test. Iso: Isoproterenol; LD: *L. draba*.

2.3. Effects of hydroalcoholic extract of *L. draba* on cardiac hypertrophy

In order to obtain the amount of cardiac hypertrophy, the ratio of heart weight (g) to body weight (kg) was calculated. The results showed that HW\BW ratio in Iso group was significantly higher than control group (P<0.001). The rats treated with *L. draba* hydroalcoholic extract at doses of 250 and 500 mg/kg reduced significantly the HW/BW ratio in comparison to Iso group (P<0.01, P<0.05 respectively) (Figure. 3).

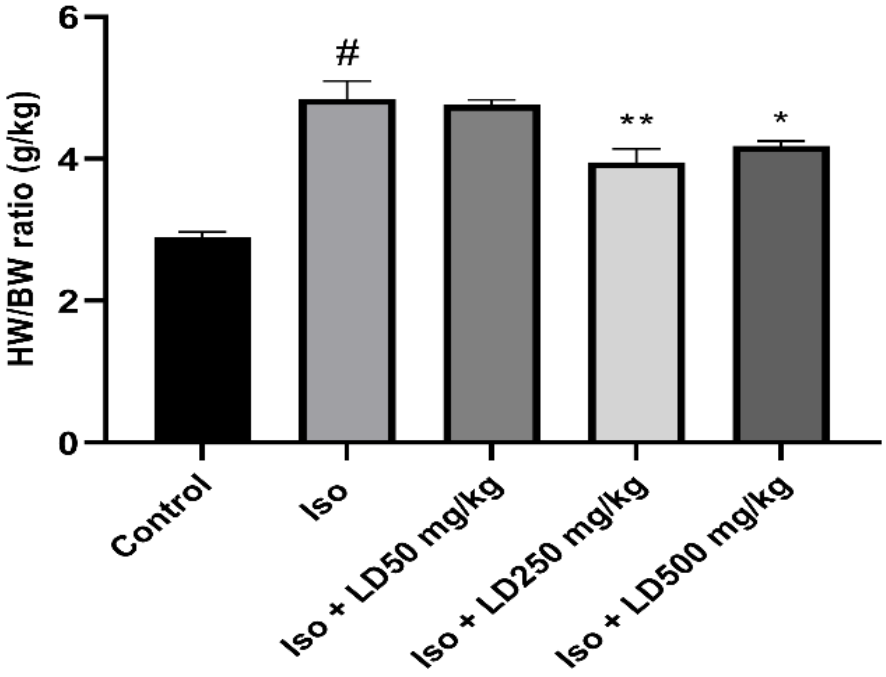

Figure 3. The effects of hydroalcoholic extract of *L. draba* at doses of 50, 250, and 500 mg/kg on heart weight (HW) to body weight (BW) ratio in isoproterenol-induced heart failure in rats. Iso: isoproterenol; LD: *L. draba*. Values are the mean ± S.E.M (n = 6); # $P < 0.001$ from respective control value, * $P < 0.05$, ** $P < 0.01$ as compared with isoproterenol treated group using one-way ANOVA with Tukey post-hoc test.

2.4. Effects of hydroalcoholic extract of *L. draba* on histopathology

Our histopathological examination demonstrated that in the control group, myocardial fibers were arranged regularly with clear striations, and there was no apparent necrosis, neutrophil infiltration (Figure 4) and glycogen (Figure 5). Heart failure (Iso) group showed widespread subendocardial necrosis, leukocyte accumulation (Figure 4) and glycogen content in comparison to control group ($P<0.001$; Figure 5). Treatment with *L. draba* extract at all three doses caused serious damage to the cardiac tissue and resulted in spongy myocardium (Figure 4). Our results also showed that administration of hydroalcoholic extract of *L. draba* (500 mg/kg) increased glycogen content in the myocardial tissue ($P<0.001$, Figure 5).

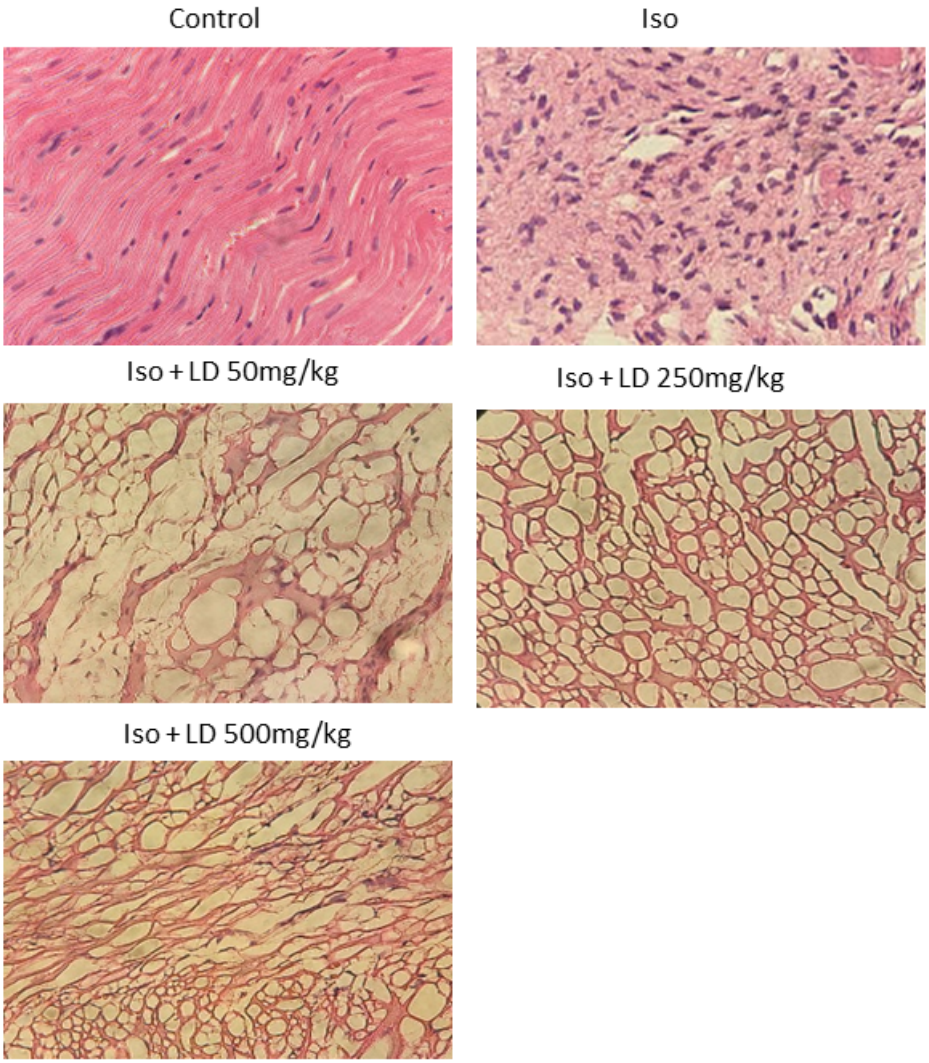

Figure 4. Photomicrographs of sections of rat cardiac apexes. Treatment with *L. draba* at three doses caused a spongy myocardium pattern. H&E (40 M).

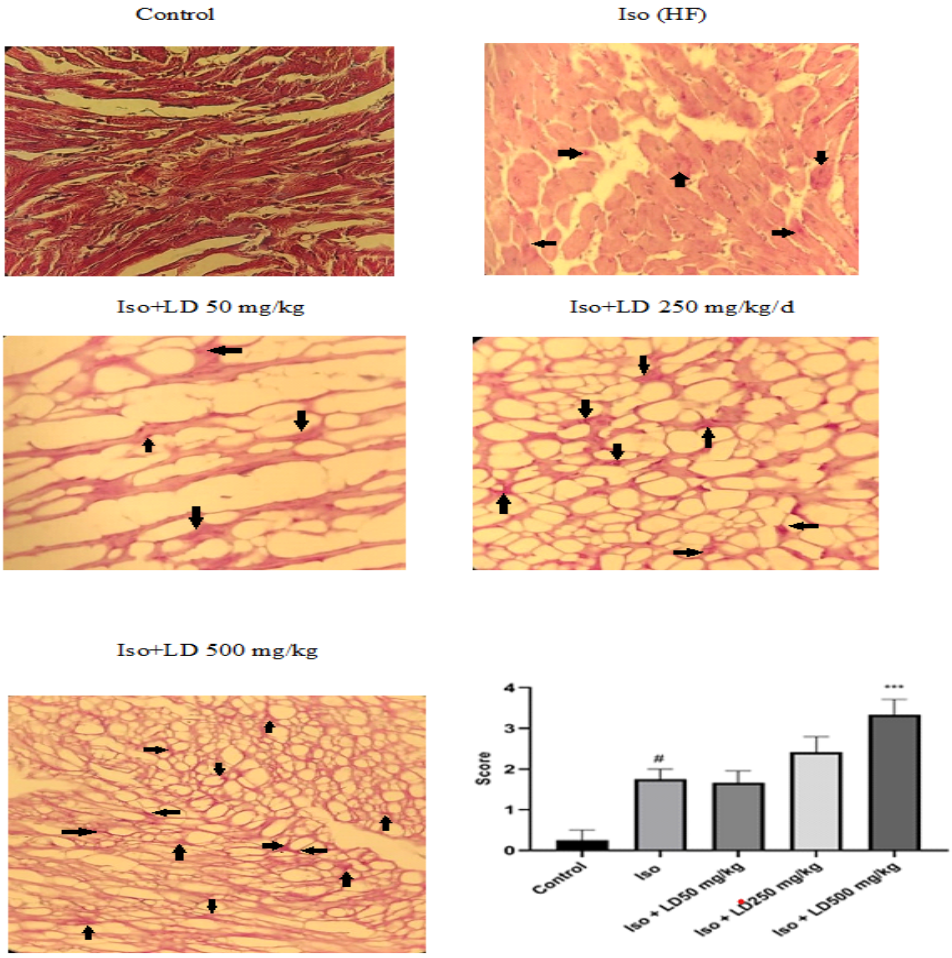

Figure 5. Photomicrographs of sections of rat myocardium after PAS staining to detect glycogen. Treatment with *L. draba* increased glycogen storage in the myocardial tissue. Iso: isoproterenol; LD: *L. draba*. Values are the mean ± S.E.M (n = 6); # P < 0.001 from respective control value, *** P < 0.001 as compared with isoproterenol treated group using one-way ANOVA with Tukey post-hoc test. PAS (40 M).

2.5. Effects of hydroalcoholic extract of *L. draba* on lactate dehydrogenase level

Induction of heart failure by isoproterenol increased the serum level of LDH from 86±8 in control group to 213±20 in Iso group (P<0.01). Treatment with *L. draba* extract (500 mg/kg) showed higher level of LDH compared with the group receiving isoproterenol alone (P<0.05) which shows the harmful and toxic effects of this extract on cells (Figure 6).

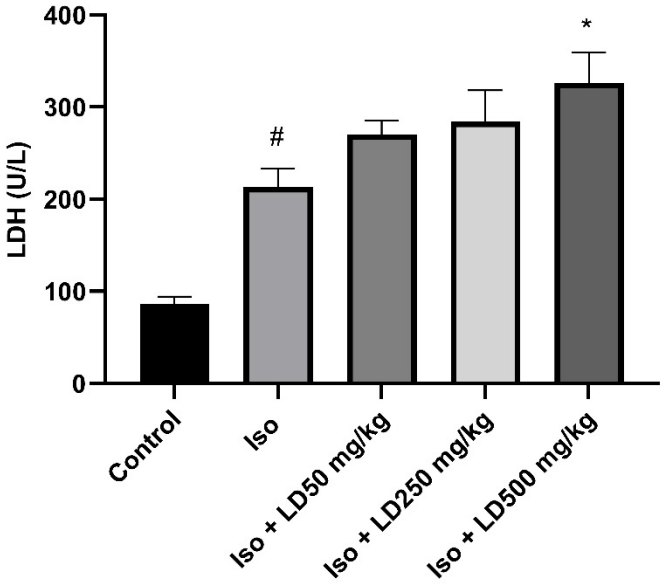

Figure 6. The effects of hydroalcoholic extract of *L. draba* at doses of 50, 250, and 500 mg/kg on LDH level in isoproterenol-induced heart failure in rats. Iso: isoproterenol; LD: *L. draba*. Values are the mean ± S.E.M (n = 6). # P < 0.01 from respective control value, * P < 0.05 as compared with isoproterenol treated group using one-way ANOVA with Tukey post-hoc test.

2.6. Effects of hydroalcoholic extract of *L. draba* on lipid peroxidation

To determine the lipid peroxidation, serum MDA level was measured. It was found that MDA level significantly increased from 6.5±0.28 in control group to 12±0.57 in Iso group (P<0.01). Our results showed that the administration of *L. draba* extract at dose of 500 mg/kg significantly increased MDA levels (P<0.01) in comparison to Iso group (Figure 7).

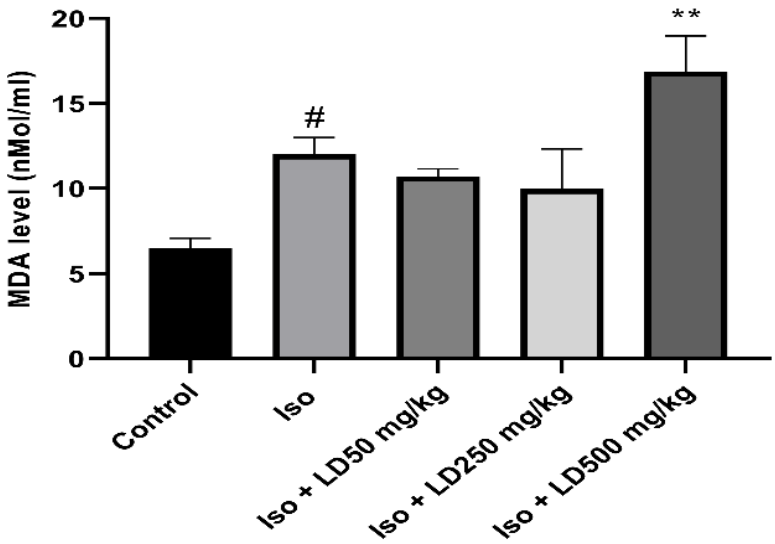

Figure 7. The effects of hydroalcoholic extract of *L. draba* at doses of 50, 250, and 500 mg/kg on MDA level in isoproterenol-induced heart failure in rats. Iso: isoproterenol; LD: *L. draba*. Values are the mean ± S.E.M (n = 6); # P < 0.01 from respective control value, ** P < 0.01 as compared with isoproterenol treated group using one-way ANOVA with Tukey post-hoc test.

3. DISCUSSION

The present study was conducted in order to evaluate the effects of hydroalcoholic extract of *L. draba* against isoproterenol-induced heart failure in rats. The results of our study showed that the administration of the hydroalcoholic extract of *L. draba* for ten days increased the amount of glycogen accumulation and tissue necrosis, as well as destruction of the heart tissue (spongy tissue). In addition, the extract increased the level of malondialdehyde and lactate dehydrogenase and did not affect hemodynamic factors and electrocardiogram. Therefore, in this study, the toxic effects of *L. draba* on heart tissue after ten days' administration are reported. It should be noted that in our previous study and investigation of the effect of this plant in myocardial infarction with short-term administration of the extract (two days), protective effects were reported [13], and it seems that the duration of administration of this extract can be decisive in the occurrence of toxic or therapeutic effects. Studies have shown that isoproterenol reduces mean arterial pressure and heart rate [14, 15]. Also, in our study, isoproterenol caused a decrease in heart rate and mean arterial pressure. Treatment with hydroalcoholic extract of *L. draba* did not affect the heart rate and mean arterial pressure of rats subjected to myocardial infarction by isoproterenol (Fig.1). A study that examined the effect of *Lepidium sativum* extract on the heart rate of rats reported that the studied plant extract did not affect the heart rate [16]. It has already been shown that ST-segment depression and reduction in R-amplitude indicates cardiac ischemia [17] and myocardial infarction [18]. R-amplitude reduction also demonstrates cardiac edema. In the present study, isoproterenol caused a ST segment depression and R-amplitude suppression. In a similar study conducted by Ren et al., with the injection of isoproterenol, ST segment depression was observed, which was at its highest during the first days of the injection [19]. Our results showed that the hydroalcoholic extract of the *L. draba* did not improve ECG pattern and only increased R-amplitude, which regarding to histopathological results it cannot be considered protective effects and this increment in R-amplitude can be attributed to cardiac tissue destruction and volume reduction. The results of the present study showed that the administration of the hydroalcoholic extract of *L. draba* for 10 days increased necrosis and tissue damage as well as increased the myocardial content and glycogen accumulation after isoproterenol-induced heart failure. In severe heart failure, glycolysis may be detrimental. Failure to dispose of glucose can lead to deleterious effects that negate the benefits of anaerobic ATP production [20, 21]. In general, studies have shown that the accumulation of glycogen in the heart at the onset of cardiac disorders is due to the protection of the heart, while the excessive accumulation of glycogen in the heart tissue leads to functional impairment of the heart [22, 23]. Other studies conducted with other plants of the *Brassicaceae* family reported the cardioprotective effects [24]. Also, in our previous study on myocardial infarction and the short-term administration of the extract for two days, the improving effects on the cardiac histopathology, including the reduction of cardiac fibrosis, were observed [13]. It seems that the extract of *L. draba* has a narrow therapeutic window and repetitive daily administration causes higher plasma concentration beyond the therapeutic window which shows damaging and toxic effects.

Supramaximal doses of isoproterenol produce acute myocardial necrosis and interstitial fibrosis [25]. In addition, isoproterenol administration causes myocardial injury, with increased plasma LDH activity and MDA content [26]. In our study, the results indicated an increase in the level of LDH in the Iso treated group. While isoproterenol itself caused a significant increase in the serum level of LDH, administration of the *L. draba* extract at high doses increased LDH level, which shows the harmful and toxic effects of this extract on cells. Lactate dehydrogenase (LDH) is an enzyme that exists intracellularly and plays a critical role in energy production. Specifically, LDH functions by catalyzing pyruvate to lactate under anaerobic conditions. Prior research has demonstrated that certain conditions, such as tissue injury, necrosis, and hypoxia, can lead to increased serum levels of LDH. Notably, LDH is a cytosolic enzyme that is capable of leaking out from damaged tissue into the bloodstream when the cell membrane exhibits permeability or ruptures. As such, the concentration of LDH present in serum is reflective of any alterations in plasma membrane permeability and/or integrity. An increase in LDH may signify cardiac damage and is therefore utilized in the diagnosis of acute myocardial infarction. LDH has also been shown to be elevated in patients with valve heart disease and heart failure and its presence is associated with an increased risk of cardiovascular mortality[27, 28].

The cardiotoxicity induced by isoproterenol was explicated through the generation of oxygen-free radicals and sulfhydryl reactivity, which were brought about by various oxidation products [29]. The oxygen-free radicals can promote lipid peroxidation, subsequently increasing membrane permeability, ultimately leading to the development of cardiac injury [30]. In the current investigation, lipid peroxidation products, including myocardial MDA, were observed to increase post-isoproterenol injection. The accumulation of these products can directly cause membrane injury of cardiac myocytes [25]. The results shown in Figure 6 indicate that, unlike low and medium doses of the extract, high doses increase the level of MDA and it seems that this effect is dose-dependent. Since MDA is a marker of cellular lipid peroxidation [29], probably the hydroalcoholic

extract of *L. draba* in high doses induces the peroxidation of cellular lipids, and this extract can be considered toxic in high doses and longtime administrations. Phytochemical analysis of *L. draba* has demonstrated the presence of various compounds including saponins, flavonoids, tannins, alkaloids, terpenoids, and Leucoanthocyanin [30, 31]. A study has reported the biphasic effect of flavonoids and their impact on oxidative stress. In this study, it was reported that flavonoids at low doses led to a significant decrease in the levels of ROS and MDA that were induced by lipopolysaccharide (LPS), while also restoring the activity of superoxide dismutase (SOD). However, a higher dosage of flavonoids was observed to have a considerable impact on cell death as a result of oxidative stress, which was evident from the upregulated levels of ROS and MDA, and the downregulated activity of SOD [32]. Additionally, a separate research study has reported on tannins' antioxidant properties and their ability to act as pro-oxidants. The study's findings suggest that tannins could induce DNA damage in freshwater mussel's digestive glands at concentrations higher than 10 µM, although lower doses (1 and 5 µM) did not contribute to the DNA damage. The study concludes that the antioxidative properties of tannins may change to pro-oxidative activities at higher concentrations [33]. As mentioned above, our results suggest that high doses (500 mg/kg) of *L. draba* can trigger oxidative stress, as demonstrated by an increase in MDA level, and can be partially attributed to the presence of flavonoids and tannins.

Although *Brassicaceae* plants are generally regarded as advantageous for human health, certain aspects of their phytochemistry can induce harmful activities. For example, tannins inhibit mammalian digestive enzymes [34]. Furthermore, S-methylcysteine sulfoxide, a non-polyphenolic component, has been found to cause severe hemolytic anemia [12]. Other components, especially erucic acid, have not been studied for effects on humans, but the results of feeding experiments on animals show harmful effects such as potential myocardial damage as well as abnormal fat accumulation [35, 36]. Additionally, glucosinolates, thiocyanate metabolites, and their hydrolysis products, such as 5-vinyloxazolidine-2-thione (guatrin), are known for their adverse effects on thyroid metabolism [37]. Since *L. draba* contains alkaloids, terpenoids, tannins, saponins, leukoanthocyanins, triterpenoids, flavonoids [38] and dimethyl sulfoxide [31], the toxic effects seen from the extract of this plant in the present study can be related to the existence of these compounds.

4. CONCLUSION

The results of our study show that the administration of hydroalcoholic extract of *L. draba* for ten days in isoproterenol-induced heart failure through the destruction of heart tissue, increase in glycogen accumulation, malondialdehyde, and lactate dehydrogenase levels demonstrate toxic effects. Therefore, it is suggested that people with cardiovascular diseases avoid long-term consumption of this plant.

5. MATERIALS AND METHODS

5.1. Animals

Thirty male Wistar rats weighing 250 ± 20 gr were utilized in this study. Rats were kept in the Animal House of Urmia University of Medical Sciences, in polypropylene cages under standard conditions (temperature 22 ± 2°C with relative humidity 50 ± 10% and 12-h light/12-h dark cycle) with ad libitum access to water and chows. During the course of this study, adherence to the principles of laboratory animal care was maintained, with all procedures being conducted in accordance with the Guide for the Care and Use of Laboratory Animals as outlined by the US National Institutes of Health (NIH Publication, 8th Edition, 2011). All animal protocols were approved by the Ethics Committee of our university (ethical code: R.UMSU.REC.1400.006).

5.2. Experimental design

Rats were randomly divided into 5 groups (N=6), including the control group, the heart failure group (Iso), and the groups receiving hydroalcoholic extract of *L. draba* at doses of 50, 250 and 500 mg/kg body weight. The rats in control group were left untreated during the experiment. Rats in the heart failure group (Iso) were injected with isoproterenol at a dose of 5 mg / kg subcutaneously for ten days to induce heart failure and the rats in the treated groups were injected intraperitoneally with hydroalcoholic extract of *L. draba* at doses of 50, 250 and 500 mg/kg for 10 days simultaneously with isoproterenol injection. At the end, various factors such as the degree of hypertrophy of cardiac tissue, structural changes of the heart including necrosis and glycogen accumulation, hemodynamic factors and ECG and the level of malondialdehyde were examined.

5.3. Plant Material

The plant was harvested in June 2020 from the north of West Azerbaijan province and its aerial parts were used for extraction. First, the aerial parts of the plants were placed in the shade to dry. Then, the plants were pulverized and were used for further experimental. The yielded herbarium sample of the *L. draba* was kept in the Tabriz faculty of Pharmacy's herbarium (No: TBZFPH1989) after approval by the Pharmacognosist (Dr. Sanaz Hamedeyazdan).

5.4. Preparation of Plant Extract

The dried powdered aerial parts of *L. draba* were defatted with *n*-hexane (5 L), followed by maceration with ethanol 70% for 5 consecutive days, and then filtered with Whatman filter paper. The yielded hydroalcoholic extracts were solvent evaporated up to complete dryness via a rotary evaporator (Heidolph, Germany) at 40 °C in the vacuum.

5.5. Hemodynamic and electrocardiogram assessments

At the end of experiment, the animals were anesthetized with a mixture of ketamine (60 mg / kg) and xylazine (10 mg/kg). Then the electrodes were connected to the animal in the Lead II position and electrocardiographic parameters recorded by the power lab system (ADInstruments, Australia). Then an incision was made in the midline of the animal's neck and after isolating the left carotid artery, a polyethylene cannula was inserted into carotid to record hemodynamic parameters including: systolic blood pressure (SBP), diastolic blood pressure (DBP), heart rate (HR), mean arterial pressure (MAP), and arterial blood pressure (ABP) [39].

5.6. Cardiac tissue hypertrophy

After hemodynamic measurement, blood samples were taken from portal vein and then the animals were euthanized with an overdose of the anesthetics and the heart was quickly removed and weighed. The ratio of heart weight to body weight (g/kg bw) was calculated to assess the rate of hypertrophy [39].

5.7. Histopathological examination

The apex of the heart was isolated at the end of the study and placed in 10% formalin and then fixed in paraffin and micrometer sections were prepared. Then, Hematoxylin and Eosin (H&E) staining was used to observe leukocyte accumulation and necrosis and PAS staining to check for glycogen accumulation. Histopathological changes were scored by two trained persons (one experienced pathologist and one trained person) and rated from 1 to 4 for respectively low, medium, high and very high injuries [39].

5.8. Lactate dehydrogenase (LDH) measurement

Lactate dehydrogenase level of serum assayed as a marker of myocardium tissue injury using standard kit. LDH level measured by enzymatic kits from Byerpoul, İran. Result represented as U/L

5.9. Malondialdehyde assay

Malondialdehyde (MDA) which is the final product of lipid peroxidation, is a marker of oxidative stress were measured according to previous method [40]. The lipid peroxide expressed as nanomole MDA production per gram heart tissue and nanomole per milliliter serum, were measured spectrophotometrically.

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Conflict of interest statement: None declared.

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