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Ameliorative Influence of Dietary Dates on Doxorubicin-Induced Cardiac Toxicity

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Abstract

Doxorubicin is a commonly used anticancer agent, which may cause cardiac toxicity. The present study designed to evaluate *Phoenix dactylofera* (dates) in doxorubicin (DXR) induced cardiac toxicity and cardiac remodeling in *Wistar albino* rats. The experimental rats procured, acclimatized and finally divided into five groups (n = 6). Group I served as normal controls, group II served as disease controls and groups 3, 4 & 5 served as therapeutic groups (*Phoenix dactylofera* 5%, 10%, and 15% respectively). Cardiac remodeling and toxicity in the rats were induced by administration of DXR (1.25 mg/kg i.p. in 16 divided doses/month). At the end of protocol, effect of *Phoenix dactylofera* on cardiac remodeling was evaluated by measuring parameters like haemodynamics, heart weight, anatomy, Troponin T, creatine phosphokinase (CPK), creatine phosphokinase-MB (CPK-MB), Lactate dehydrogenase (LDH), serum glutamate oxaloacetate transaminase (SGOT), serum glutamate pyruvate transaminase (SGPT), calcium ion Ca^{2+}, sodium ion Na^{+}, potassium ion K^{+}, intracellular enzymes like Malondialdehyde (MDA), glutathione (GSH), superoxide dismutase (SOD) and catalase (CAT). The disease control groups showed significantly elevated ($p < 0.001$) levels of troponin T, CPK, CPK-MB, LDH, MDA, and significantly reduced levels ($p < 0.001$) of GSH, SOD & CAT while the levels of SGPT, SGOT were increased less significantly ($p < 0.01$) as compared to therapeutic groups. Treatment with *Phoenix dactylofera* significantly ($p < 0.01$) reduced the increased levels of Troponin T, CPK, CPK-MB, LDH, SGOT, SGPT, MDA, GSH, SOD & CAT as well as restored Ca^{2+}, Na^{+}, K^{+} levels to a normal value. Further, the histological studies of the cardiac tissues demonstrated that the normal architecture of the cardiac cells was restored in the animals fed

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with dietary *Phoenix dactylofera* as compared to disease controls. The findings show that the administration of *Phoenix dactylofera* has the potential to prevent the toxicity induced by doxorubicin in the experimental rats.

Keywords

Cardiac Remodeling, *Phoenix dactylofera*, Biochemical Parameters, Protection, Doxorubicin

1. Introduction

Cardiac dysfunction is defined as an alteration in the relationship between preload (often defined by left ventricular filling pressure) and stroke volume. This relationship is depicted by Frank-Starling curves, which identify a shift downward and to the right as cardiac dysfunction [1]. Remodeling is defined as an alteration in the structure (dimensions, mass, shape) of the heart (called cardiac or ventricular remodeling) in response to hemodynamic load and/or cardiac injury in association with neurohormonal activation. Remodeling may be described as physiologic or pathologic [2]. The remodeling process frequently includes increases in myocardial mass. The heart can respond to environmental stimuli by growth (increased myocardial mass) or shrinkage (atrophy) with a dynamic range of at least 100 percent [3]. Myocardial hypertrophy is most properly defined as increased cardiomyocyte size which may occur with or without an increase in overall myocardial mass; however, the term "hypertrophy" has also been used to denote increased myocardial mass and/or wall thickness. Physiologic remodeling is a compensatory change in the dimensions and function of the heart in response to physiologic stimuli such as exercise and pregnancy. This type of remodeling is seen in athletes and has been called athlete's heart [3]. Pathologic remodeling may occur with pressure overload (e.g., aortic stenosis, hypertension), volume overload (e.g., valvular regurgitation), or following cardiac injury (e.g., myocardial infarction, myocarditis, or idiopathic dilated cardiomyopathy). In each of these settings, remodeling may transition from an apparently compensatory process to a maladaptive one [3].

Phoenix dactylifera L. commonly known as the date palm is an important plant in the scorched regions of Southwest Asia and North Africa. The fruits which are the most commonly used part are a primary source of nutrition, especially in the arid areas where due to the extreme conditions, very few plants can grow [4]. Date fruit consists of 70% carbohydrates, most of which is in the form of sugars. Because of this, the fruits are a high source of energy and it is approximated that 100 g of the flesh can provide 314 kcal of energy [4]. Drying of date decreases the water activity, and this increases the sugar concentration. Because of this, the shelf life of dry dates are high and are available for extended periods of time [5]. The fruits are also used as a sweetener in the preparation of beer [5]. In Saudi Arabia, it is most widely used dietary food. Phytochemical investigations have revealed that the fruits contain anthocyanins, phenolics, sterols, carotenoids, procyanidins and flavonoids, compounds known to possess multiple beneficial effects. Preclinical studies have shown that the date fruits possess free radical scavenging, antioxidant, antimutagenic, antimicrobial, anti-inflammatory, gastroprotective, hepatoprotective, nephroprotective, anticancer and immunostimulant activities [6] [7]. Problems associated with the cardiovascular system are prevalent in Saudi Arabia and still need exploration to overcome these challenges [8] [9].

Doxorubicin an anthracycline antibiotic has been widely used for the treatment of a variety of cancers such as breast cancers, carcinoma of small cells of lungs and leukemias [10]. However, the use of doxorubicin is limited because of its acute and chronic toxicities. The acute toxicities are myelosuppression, nausea, vomiting and arrhythmias are reversible while the chronic toxicities such as cardiomyopathy and heart failure are irreversible and unmanageable [11]. The exact mechanism is still not known but the possible mechanisms have been postulated by the various researchers such as generation of oxidative stress [12], induction of apoptosis [13], activation of renin-angiotensin system (RAAS) [14], oxidative stress induced DNA damage [15], lipid peroxidation and impairment of enzyme activity of creatinine kinase [16] [17]. Several drugs have been evaluated for the treatment of doxorubicin-induced cardiomyopathy by various researchers. Therefore by reviewing above and many more literature in doxorubicin-induced cardiomyopathy and cardiac failure and the use of dietary supplement *Phoenix*

dactylofera in the treatment of various disease and for the inhibition of different disease inducing endogenous substances, here the present study designed to evaluate the ameliorative potential of the *Phoenix dactylofera* in doxorubicin-induced cardiomyopathy and cardiac failure.

2. Material and Methods

2.1. Experimental Animals

Laboratory-bred *Wistar* albino rats weighing 150 - 200 g at age 6 - 8 weeks of either sex were procured and housed six per cage under standard laboratory conditions at a room temperature 22˚C ± 2˚C with 12 h light/dark cycle. The animals were purchased from the animal facility of the pharmacology department, Siddartha Institute of Pharmacy, Dehradun. The animals provided with normal pellet diet water *ad libitum* and acclimatized for one week. All experiments conducted between 09:00 and 17:00 h. The experimental protocol was approved by Institutional Animal Ethics Committee of Siddhartha Institute of Pharmacy, Dehradun and all the experimental procedure used were as per guidelines of Committee for the Purpose of Control and Supervision of Experimental Animals (CPCSEA), New Delhi.

2.2. Drugs and Chemicals

Doxorubicin was purchased from MAX health care Dehradun, India. *Phoenix dactylofera* was purchased from the local market of Makkah, Saudi Arabia. All the other drugs and chemicals utilized were of analytical grade.

2.3. Experimental Design

After acclimatization, the animals were divided randomly into five groups (n = 6) and treatment schedule was as follows: Group1 rats served as normal controls and fed with normal diet during the whole study, group 2 rats served as disease controls administered with Doxorubicin 1.25 mg/kg i.p. in 16 divided doses/month. Group 3, 4 and 5 rats served as therapeutic groups which were administered with Doxorubicin 1.25 mg/kg IP in 16 divided doses/month and treated with *Phoenix dactylofera* (5%, 10% and 15% in diet respectively for one month).

After 24 h of the last dose of Doxorubicin, blood samples were collected from retro-orbital plexuses under light ether anesthesia from all experimental rats under study. The enzymatic parameters (LDH, SGPT, SGOT, Na^+, Ca^{2+} and K^+) were estimated in blood. Troponin-T, CPK, CK-MB, were estimated using test strips. Heart excised, washed in ice-cold physiological saline, a small portion of heart was weighed and homogenized for biochemical estimations (malondialdehyde [MDA], glutathione [GSH], superoxide dismutase [SOD] and catalase [CAT]). Remaining part of the heart preserved in phosphate buffer (strength 100 mM, PH 7.4) for histological studies.

2.4. Hemodynamic Measurements

Hemodynamic measurements were done by tail cuff method on Biopac Non-Invasive Blood Pressure Recording Instrument (USA). All the rats trained in the restrainer initially for 15 min every day at least 10 - 15 days before the day of measurement of the hemodynamic parameters (systolic, diastolic, mean blood pressure and heart rate) and then the final measurement were done.

2.5. Biochemical Estimation in Serum

Creatine phosphokinase, Troponin-T, Creatine kinase myocardial band isoenzyme (CK-MB) were estimated using the test strips, while LDH, SGPT, SGOT, Na^+, Ca^{2+} and K^+ were estimated in serum by enzymatic kits using biochemistry semi auto analyzer, Nicholas Piramal 5010.

2.6. Biochemical Assay in Cardiac Tissues Homogenates

Measurement of lipid peroxidation was done as per the method of Ohkawa [18]. Antioxidant enzymes GSH, SOD, and CAT, were determined in cardiac tissue as per standard protocol. GSH estimated by Ellman method, Activity of SOD measured by the method of Marklund, CAT activity was measured according to the method of Clairbone [19].

2.7. Histology

Samples fixed in modified Karnovasky's solution and buffered in 0.1 M sodium phosphate buffer (pH 7.4). Fixation was done for 8 to 12 h at 4˚C then the tissues washed with 0.1 M sodium phosphate buffer. After several washings specimens desiccated in graded acetone solutions and rooted in CY212 Araldite. Thin sections of 60 to 80 nm thickness were incised using microtome, and the sections were stained with alcoholic uranyl acetate (10 min) and lead citrate (10 min) then the histological studies performed.

2.8. Statistical Analysis

Results were expressed as mean ± standard error of mean (S.E.M.). Groups of data were compared with the analysis of variance (ANOVA) followed by Dunnett's t-test. Values were considered statistically significant at $P < 0.05$, 0.01 and 0.001 respectively.

3. Results

3.1. Hemodynamic Parameters

The systolic, diastolic, mean blood pressure and heart rate were found significantly ($P < 0.01$) increased in disease control group (group 2) as compared to the normal control group (group I) while treatment of *Phoenix dactylofera* (5%, 10% and 15% respectively) in diet (group 3, 4 and 5) caused significant ($P < 0.05$; $P < 0.01$; $P < 0.001$) reduction in group 3 and 4. The dietary treatment with *Phoenix dactylofera* (10% completely restored the systolic, diastolic, mean blood pressure and heart rate as compared to the doxorubicin control group (**Table 1**, **Figure 1**).

3.2. Creatine Kinase, Troponin T, Creatine Kinase Myocardial Band Isoenzyme (CK-MB) and Lactate Dehydrogenase (LDH) Activities

Treatment of rats with DXR (1.6 mg/kg in 16 divided doses/month, i.p.) caused a significant ($P < 0.01$; $P < 0.001$) increase in both serum CK, troponin T, CK-MB and LDH enzyme activities as compared to their respective values in normal controls. Dietary intake of *Phoenix dactylofera* (10%) significantly ($P < 0.01$) reduced their elevated levels and restored them almost to normal (**Table 2**, **Figure 2(a)** & **Figure 2(b)**).

3.3. Serum SGOT, SGPT, Na^+, Ca^{2+} and K^+

The significant elevations ($P < 0.01$; $P < 0.001$) found in serum SGOT, SGPT levels of the disease controls as compared to normal controls. Dietary intake of *Phoenix dactylofera* caused the significant ($P < 0.01$) reduction. The significant results were observed in the animals fed with *Phoenix dactylofera* (10%). There were no significant alterations found in the levels of serum Na^+, Ca^{2+} and K^+ in both normal controls, disease controls and therapeutic controls (**Table 3**, **Figure 3**).

3.4. Lipid Peroxidation (Malondialdehyde [MDA])

Lipid peroxide levels were determined by evaluating myocardial MDA content. MDA levels were significantly ($P < 0.01$; $P < 0.001$) higher in the doxorubicin control group (Group 2) as compared to normal controls (Group 1).

Table 1. Effect of dates on different hemodynamic parameters.

Experimental Groups	Systolic BP (mm Hg)	Diastolic BP (mm Hg)	Mean BP (mm Hg)	Heart rate (beats/min)
Normal Control	135.3 ± 1.36	91.55 ± 0.98	115.44 ± 0.79	376.44 ± 3.90
Doxorubicin Control	196.3 ± 2.47^{B}	121.57 ± 1.40^{B}	179.22 ± 1.30^{B}	521.11 ± 3.08^{B}
Dates Control (5%)	174.1 ± 2.40^{b}	105.98 ± 1.36^{b}	154.10 ± 0.77^{c}	412.10 ± 3.82^{b}
Dates Control (10%)	149.7 ± 1.81^{b}	99.99 ± 1.05^{c}	124.02 ± 0.90^{b}	387.20 ± 3.78^{a}
Dates Control (15%)	155.8 ± 2.01^{c}	101.04 ± 1.03^{c}	125.91 ± 0.50^{b}	438.29 ± 3.30^{b}

^{a} = $P < 0.05$, ^{b} = $P < 0.01$, and ^{c} = $P < 0.001$ compared to doxorubicin control; whereas ^{B} = $P < 0.01$as compared to normal control. a = *, b = ¶, c = +, B = # (as shown in **Figure 1**).

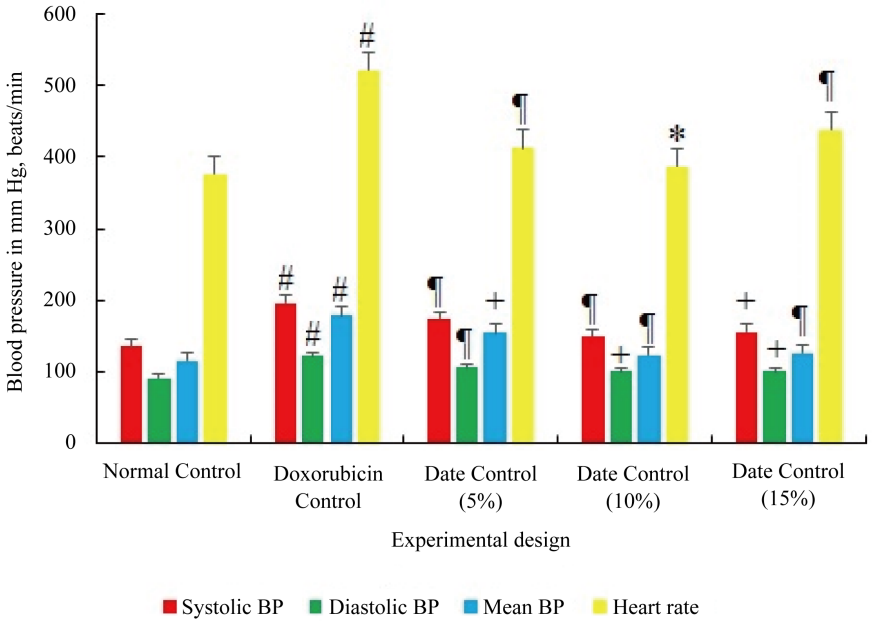

Figure 1. The effect of *Phoenix dactylofera* on blood pressure and heart rate in mice: Each trial was performed in triplicate. The data were expressed as Mean ± S.E.M. Where n = 6 in each group. P-value < 0.05, 0.01, and 0.001 were considered statistically significant as compared to Doxorubicin control; whereas P-value < 0.01 as compared to Normal Control (one-way ANOVA followed by Tukey's post-test). BP = Blood pressure. For systolic, diastolic and mean BP, the measuring units were expressed in mm Hg on Y-axis, while the heart beat was measureed in beats/minute. P < 0.05 = *, P < 0.01 = ¶, P < 0.001 = +, P < 0.01= #.

Table 2. Effect of dates on different biochemical parameters.

Experimental Groups	Troponin T (U/L)	CPK (U/L)	CPK-MB (U/L)	LDH (U/L)
Normal Control	0.31 ± 0.01	155.48 ± 2.67	88.49 ± 0.89	83.40 ± 0.81
Doxorubicin Control	2.32 ± 0.11^{B}	475.49 ± 3.30^{C}	199.01 ± 1.87^{B}	319.10 ± 3.09
Dates Control (5%)	0.42 ± 0.03^{b}	181.22 ± 1.31^{b}	95.32 ± 1.03^{b}	93.20 ± 0.88
Dates Control (10%)	0.37 ± 0.01^{b}	164.79 ± 1.05^{b}	85.02 ± 0.66^{b}	89.01 ± 0.88
Dates Control (15%)	0.36 ± 0.02^{c}	165.55 ± 1.06^{b}	86.30 ± 0.45^{b}	91.31 ± 1.02^{b}

^{a} = P < 0.05, ^{b} = P < 0.01, and ^{c} = P < 0.001 compared to doxorubicin control; whereas ^{B} = P < 0.01, and ^{C} = P < 0.001 as compared to normal control. Where a = *, b = ¶, c = +, B = #, C = × as shown in **Figure 2(a)**, **Figure 2(b)**.

Table 3. Effect of dates on serum SGOT, SGPT, Calcium, sodium and potassium of animals.

Experimental Groups	SGPT (mg/dl)	SGOT (mg/dl)	Ca^{2+} (mg %)	Na^{+} (m.eq/L)	K^{+} (m.eq/L)
Normal Control	49.99 ± 046	55.23 ± 1.04	9.01 ± 0.03	6.66 ± 0.15	9.88 ± 0.14
Doxorubicin Control	79.29 ± 0.59^{B}	80.10 ± 0.92^{C}	14.09 ± 0.11^{B}	7.9 ± 0.18^{B}	6.67 ± 0.13
Dates Control (5%)	66.10 ± 0.69^{a}	48.33 ± 0.77^{a}	10.12 ± 0.12^{b}	6.51 ± 0.10^{b}	8.89 ± 0.18
Dates Control (10%)	44.40 ± 0.13^{b}	54.23 ± 0.66^{b}	9.55 ± 0.09^{b}	6.59 ± 0.12^{b}	9.02 ± 0.21
Dates Control (15%)	50.11 ± 0.50^{b}	40.29 ± 0.22^{c}	10.41 ± 0.07^{b}	5.98 ± 0.15^{b}	8.81 ± 0.32^{b}

^{a} = P < 0.05, ^{b} = P < 0.01, and ^{c} = P < 0.001 compared to doxorubicin control; whereas ^{B} = P < 0.01, and ^{C} = P < 0.001 as compared to normal control and a = *, b = ¶, c = +, B = #, C = × as shown in **Figure 3**.

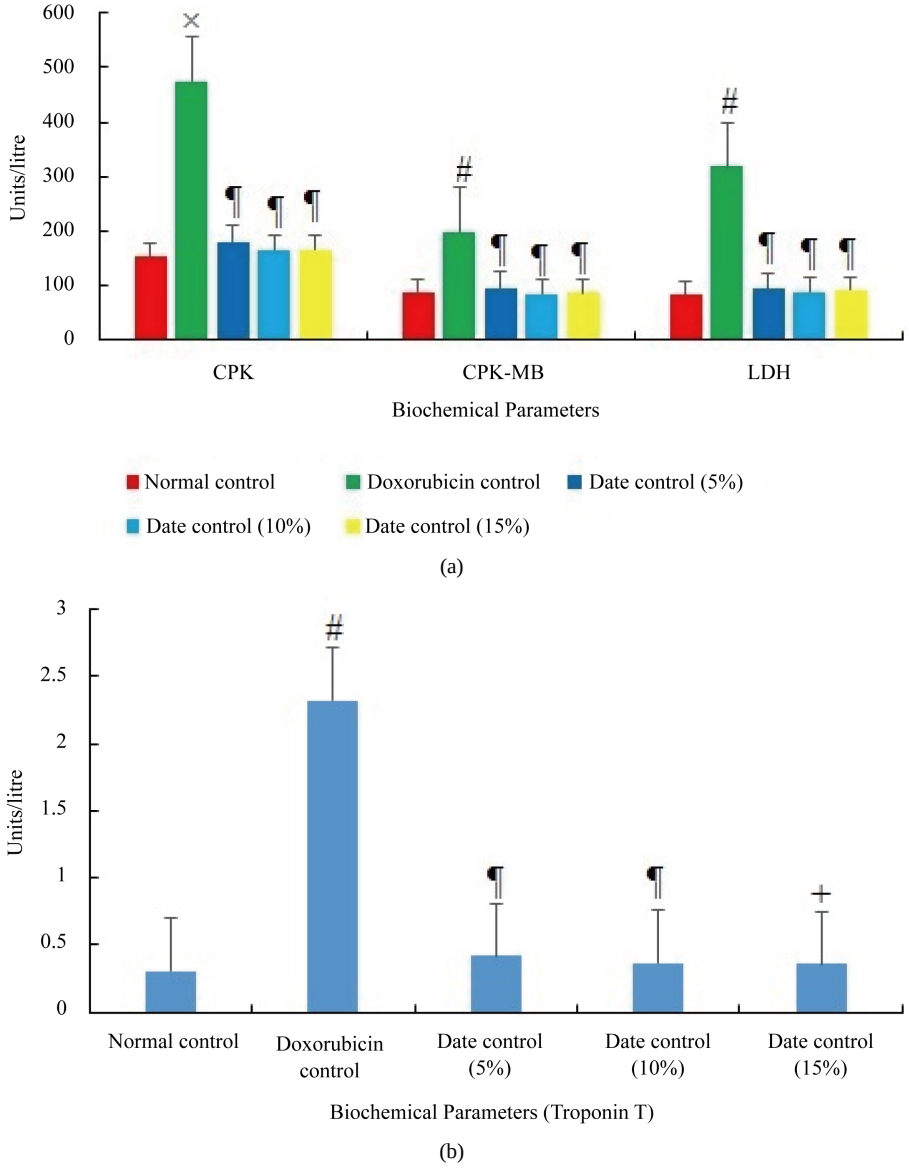

Figure 2. (a) The CPK, CPK-MB and LDH levels in mice treated with *Phoenix dactylofera*: Each trial was performed in triplicate. The data were presented as Mean ± S.E.M. Where n = 6 in each group. P-value < 0.05, 0.01, and 0.001 were considered statistically significant as compared to Doxorubicin control; whereas P-value < 0.01 as compared to Normal Control (one-way ANOVA followed by Tukey's post-test). CPK = Creatine phosphokinase, CPK-MB = Creatine phosphokinase myocardial band, LDH = Lectate dehydrogenase. P < 0.05 = *, P < 0.01 = ¶, P < 0.001 = +, P < 0.01 = #, P < 0.001 = ×. (b) Troponin T level in mice treated with *Phoenix dactylofera*: Each trial was performed in triplicate. The data were presented as Mean ± S.E.M. Where n = 6 in each group. P-value < 0.05, 0.01, and 0.001 were considered statistically significant as compared to Doxorubicin control; whereas P-value < 0.01 as compared to Normal Control (one-way ANOVA followed by Tukey's post-test). P < 0.01 = ¶, P < 0.001 = +, P < 0.01 = #.

MDA levels were found significantly (P < 0.05; P < 0.01; P < 0.001) decreased in the *Phoenix dactylofera* (5%, 10% and 15%) treated groups (group 3 and 4 and 5) as well as the MDA level was also found decreased significantly (P < 0.05; P< 0.01) in *Phoenix dactylofera* (10%) fed group (**Table 4**, **Figure 4**).

3.5. Antioxidant Enzymes

The Doxorubicin control group showed significantly increased CAT while GSH and SOD were significantly

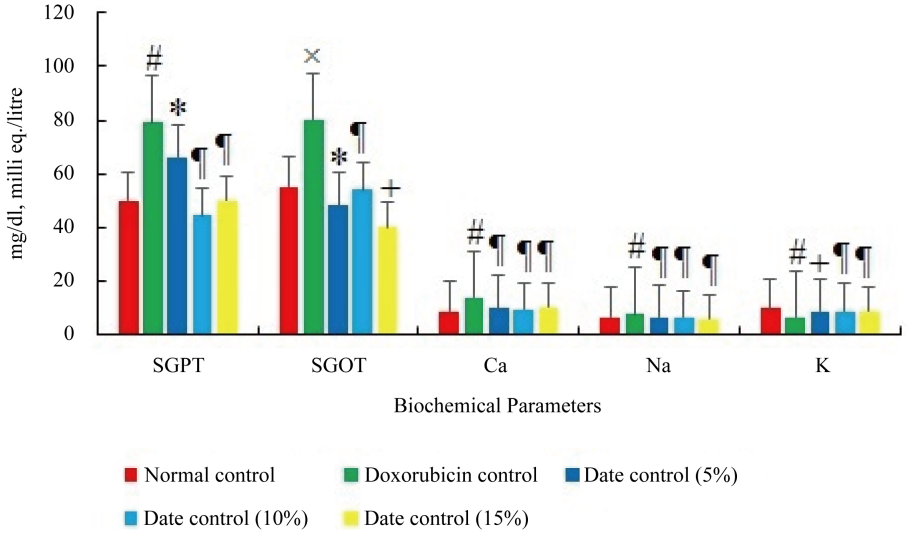

Figure 3. The serum SGPT, SGOT and serum electrolyte values in mice treated with *Phoenix dactylofera*: Each trial was performed in triplicate. The data were presented as Mean ± S.E.M. Where n = 6 in each group. P-value < 0.05, 0.01, and 0.001 were considered statistically significant as compared to Doxorubicin control; whereas P-value < 0.01 and <0.001 as compared to Normal Control (one-way ANOVA followed by Tukey's post-test). SGPT = serum glutamate pyruvate transaminase, SGOT = serum glutamate oxaloacetate transaminase. The serum SGPT, SGOT were measured in mg/dl, serum Ca^{2+} was determined in mg %, while Na^{+} and K^{+} were determined in milli eq./litre. P < 0.05 = *, P < 0.01 = ¶, P < 0.001 = +, P < 0.01 = #, P < 0.001 = ×.

Table 4. Effect of dates on antioxidant enzyme levels in rats.

Experimental Groups	MDA ((nM/mg protein)	GPx (µM of GSH/min/mg protein)	CAT (µM of H_2O_2/min/mg protein)	SOD (U/mg protein)
Normal Control	3.17 ± 0.22	26.22 ± 0.57	134.30 ± 1.14	8.19 ± 0.08
Doxorubicin Control	1.66 ± 0.11^{B}	10.50 ± 0.08^{B}	79.36 ± 0.59^{C}	4.55 ± 0.33^{C}
Dates Control (5%)	3.34 ± 0.19^{a}	19.11 ± 0.10^{c}	99.05 ± 0.71^{c}	5.20 ± 0.28^{b}
Dates Control (10%)	3.01 ± 0.40^{b}	20.89 ± 0.32^{a}	126.50 ± 0.33^{b}	7.99 ± 0.49^{a}
Dates Control (15%)	2.79 ± 0.41^{c}	21.87 ± 0.87^{b}	117.49 ± 0.81^{a}	7.01 ± 0.19^{c}

^{a} = P < 0.05, ^{b} = P < 0.01, and ^{c} = P < 0.001 compared to doxorubicin control; whereas ^{B} = P < 0.01, and ^{C} = P < 0.001 as compared to normal control and a = *, b = ¶, c = +, B = #, C = × as shown in **Figure 4**.

decreased as compared to normal controls. Treatment with *Phoenix dactylofera* 10% in the diet significantly restored the levels of antioxidant enzymes towards normal value as compared to other therapeutic groups too. (**Table 4**, **Figure 4**).

3.6. Histopathological Examinations

Histopathological photographs of normal control myocardial cells showed normal nucleus, myofibril, and mitochondria (**Figure 5(a)**). In doxorubicin-treated disease control group showed vacuolation of the endoplasmic reticulum, swelling of mitochondria with disrupt cristae, broken nuclear membrane, condensation and margination of nuclear chromatin at the nuclear membrane and nucleus (**Figure 5(b)**). Dates treated group showed homogeneous chromatin and normal structure of the nucleus and nuclear membrane (**Figures 5(c)-(e)**).

4. Discussion

Doxorubicin (DXR) is one of the most important chemotherapeutic substitutes for solid tumors such as carcinomas of breast and lung, and soft tissue sarcomas [10]. Due to severe toxic effects and development of cardiomyopathy and cardiac failure the use of DXR is limited [11]. Although the mechanism for the development of

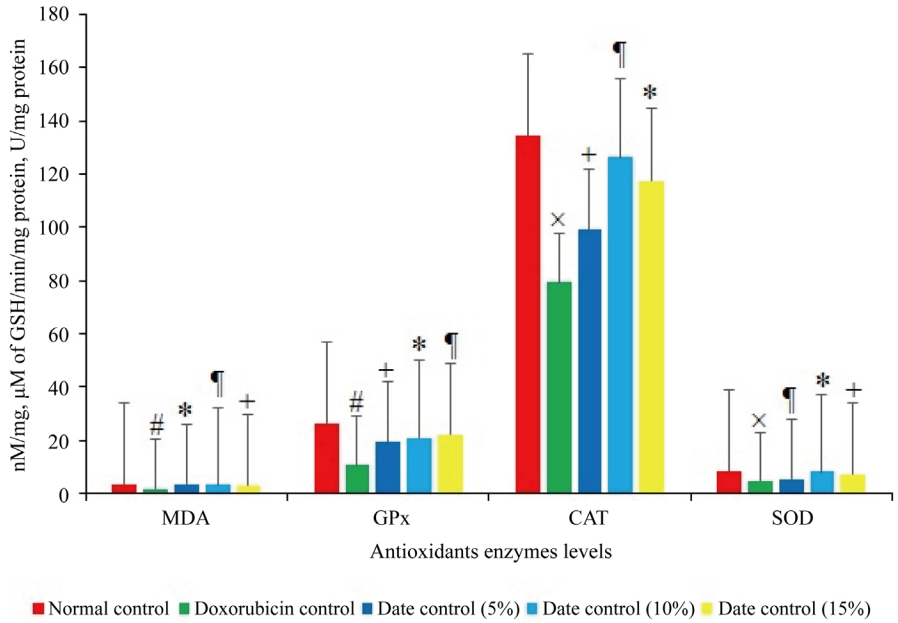

Figure 4. The antioxidant enzyme levels in mice treated with *Phoenix dactylofera*: Each trial was performed in triplicate. The data were presented as Mean ± S.E.M. Where n = 6 in each group. P-value < 0.05, 0.01, and 0.001 were considered statistically significant as compared to Doxorubicin control; whereas P-value < 0.01 and <0.001 as compared to Normal Control (one-way ANOVA followed by Tukey's post-test). MDA = Malondialdehyde, GPx = Glutathione Peroxidase, CAT = Catalase, SOD = Superoxide dismutase, The MDA concentration was measured in nanoMole/mg of protein, GPx was determined in µM of GSH/min/mg protein, CAT was measured in µM of H_2O_2/min/mg protein, and SOD was measured in U/mg of protein. P < 0.05 = *, P < 0.01 = ¶, P < 0.001 = +, P < 0.01= #, P < 0.001 = ×.

cardiomyopathy is not well understood still DXR is well-established drug for the induction of cardiac toxicity which ultimately lead to cardiac remodeling by various mechanism such as ROS generation [20], Increasing Ca^{2+} overload in the cardiocytes [21], metabolite accumulation [22], stimulating the production of prostaglandins [23] and thromboxanes, stimulating histamine release [24], indirect interaction with the actin–myosin contractile system in the heart by both positive ionotropic [25] and negative ionotropic effects [26]. Here in the present research protocol, it has been confirmed again that DXR in 16 equal cumulative doses (1.25 mg/kg i.p.) has the capability to induce chronic cardiomyopathy in rats which substantiate the findings of the previous researchers.

Earlier the researchers worked and stated that the administration of DXR causes an alteration in the systolic, diastolic and mean blood pressure, as well as heart rate [27]. The present research study also demonstrated the significant increase (P < 0.01) of systolic, diastolic, mean blood pressure and heart rate in the disease control rats as compared to normal controls (**Table 1**, **Figure 1**). Moreover, the decrease in body & heart weights certifies the claims of the previous investigators [28]. These findings may be due to the deleterious effects on intestinal mucus membrane which had led to decreasing food intake and reduced secretions of intestinal hormones [29]. Results of the present research demonstrate that administration of *Phoenix dactylofera* restored the hemodynamics (systolic, diastolic and mean blood pressure and heart rate) towards normal value (**Table 1**). Furthermore, the body and heart weight were also found maintained towards normal value in the animals fed with *Phoenix dactylofera*.

Further serum levels of troponin T, CK, CK-MB and LDH are important myocardial enzymes for the evaluation of cardiotoxicity and congestive heart failure [30]. A number of scientists found the elevation of serum troponin T, CK, CK-MB and LDH during the cardiotoxic events. In the present research protocol, serum levels of these enzymes were also found significantly increased in the disease control group, whereas dietary intake of *Phoenix dactylofera* prevented this increase markedly, indicating cardioprotective efficacy against DXR toxicity (**Table 2**, **Figure 2(a)** & **Figure 2(b)**).

Scientists have observed and proved already the involvement of ROS in the generation of myocardial injury and congestive cardiac failure [31]. Our findings demonstrate that The DXR exposure lead to the significant increment in ROS generation in cardiomyocytes and exhibited a significant (P < 0.01) rise in the MDA and CAT

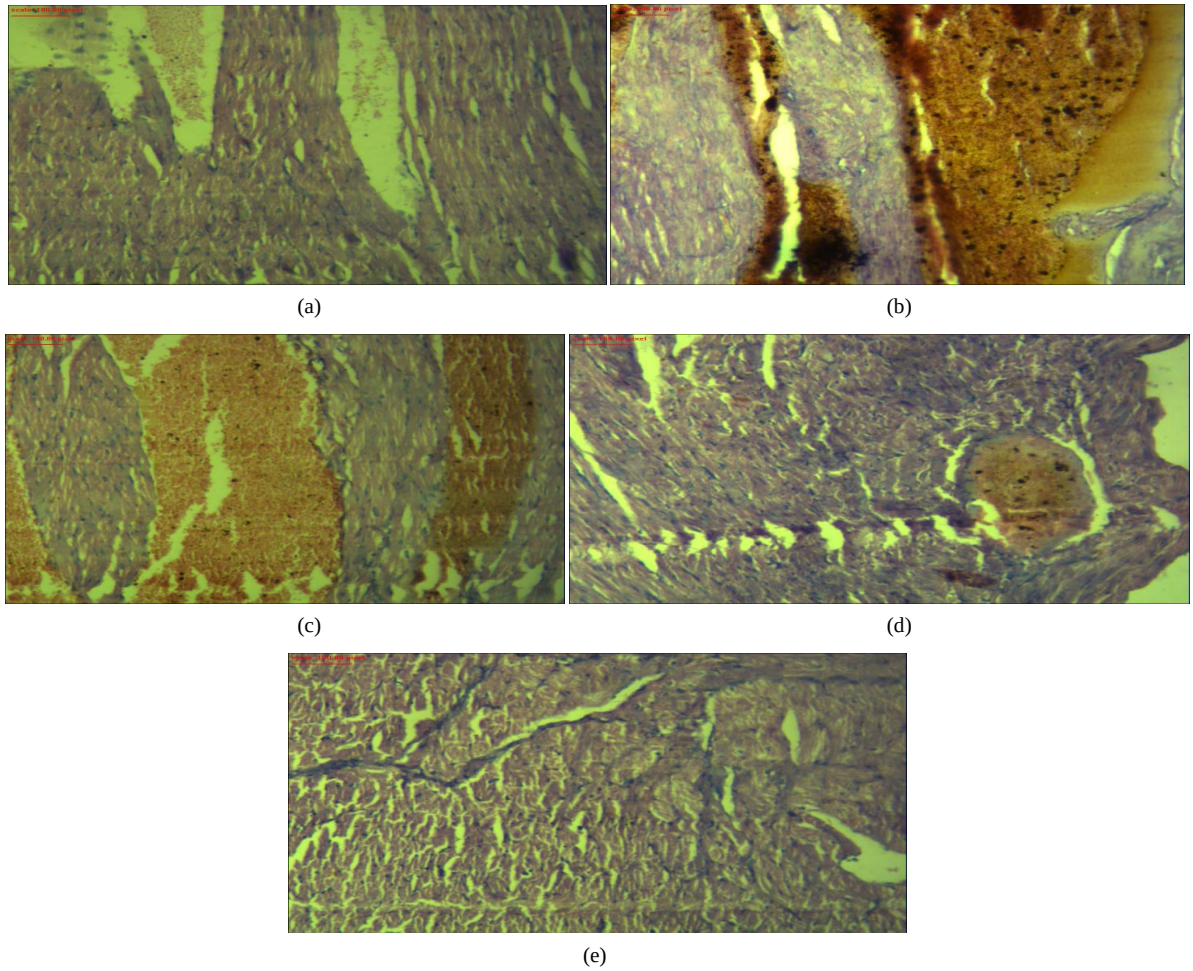

Figure 5. Histopathological studies showing morphological changes in rat cardiomyocytes: (a) In normal control, rat cardiomyocytes shows regular nucleus and intact myofibril and mitochondria; (b) In doxorubicin (1.25 mg/kg in 16 divided doses/month) treated rats, cardiomyocytes showed vacuolation of the endoplasmic reticulum, swelling of mitochondria with disrupt cristae, broken nuclear membrane, condensation and margination of nuclear chromatin at the nuclear membrane and nucleus; (c)-(e) Phoenix dactylofera (5% - 15% in diet) treated rats showed an altered architecture of the cardiomyocytes with homogeneous chromatin and normal structure of the nucleus and nuclear membrane indicating restoration of normal cardiomyocytes morphology and physiology.

concentration and a significant ($P < 0.01$) reduction in the activity of GSH and SOD in cardiac tissue of disease control animals (**Table 3**, **Table 4**, **Figure 3**, **Figure 4**).

Animals fed with dietary *Phoenix dactylofera* found to have decreased MDA and CAT levels and an improvement in GSH and SOD levels which confirms our claim that *Phoenix dactylofera* has the antioxidant effect in DXR-induced cardiomyopathy (**Table 4**, **Figure 4**). Histological examinations demonstrated an altered architecture of the cardiomyocytes of the diseased control animals which were found to be restored in the animals fed with the *Phoenix dactylofera* (**Figures 5(a)-(e)**).

5. Conclusion

Findings of the research demonstrate that dietary intake of *Phoenix dactylofera* has the pronounced preventive effect on the cardiotoxicity of doxorubicin. Further administration of nutraceutical has the marked influence on the various parameters of importance related to cardiotoxicity. Hence, therefore, it can be concluded that co-administration of *Phoenix dactylofera* with diet is well capable of reducing the incidents of cardiotoxicity.

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