RESEARCH ARTICLE

Haemato-Biochemical Alterations following Doxorubicin Induced Cardio-Renal Toxicity and Amelioration by Hesperidin in Male Wistar Rats

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Abstract

Doxorubicin is an effective anthracycline chemotherapeutic agent, but its clinical use is limited by dose dependent toxicity involving multiple organs, particularly the heart and kidneys. The present study was undertaken to evaluate the effects of doxorubicin on clinical manifestations, feed intake, body weight, organ index, haematological and serum biochemical parameters in Wistar rats and to assess the ameliorative potential of hesperidin in comparison with benazepril. Forty rats were randomly allocated into five groups of eight animals each. Group I served as control and received 0.5% carboxymethyl cellulose orally daily for 28 days. Groups II to V received doxorubicin intraperitoneally at 2.5 mg/kg body weight once weekly for four weeks. Group III additionally received benazepril at 10 mg/kg/bw orally, while Groups IV and V received hesperidin orally at 100 mg/kg/bw and 200 mg/kg/bw body weight, respectively, daily for 28 days. Doxorubicin treated rats exhibited diarrhoea, lethargy, reduced locomotor activity, scruffy fur, chromodacryorrhoea, red urine, decreased feed intake, reduced terminal body weight, increased relative heart and kidney weights, anaemia, leukopenia, lymphopenia and significant increase in serum cholesterol, creatinine and blood urea nitrogen. Hesperidin ameliorated these alterations in a dose dependent manner, with the higher dose showing better protective efficacy. These findings indicate that hesperidin exerts substantial ameliorative effects against doxorubicin induced cardio-renal toxicity in Wistar rats.

Keywords: Doxorubicin, Haematological parameters, Hesperidin, Organ index, Serum biochemical parameters, Wistar rat.

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Introduction

Cancer remains a major cause of morbidity and mortality worldwide in both humans and animals. Chemotherapy continues to be a cornerstone of cancer management and among the available antineoplastic agents, doxorubicin occupies an important place because of its broad spectrum efficacy against both haematological and solid malignancies. It is widely used in human and veterinary oncology against conditions such as lymphoma, haemangiosarcoma, mammary gland carcinoma and several solid tumours (Fullerton, 2017). However, despite its proven therapeutic value, the clinical use of doxorubicin is substantially limited by cumulative and dose-dependent toxic effects, particularly involving the cardiovascular and renal systems along with haematological alteration and systemic adverse reactions (Sheibani *et al*., 2022). These toxicities markedly affect treatment safety and may compromise long term therapeutic success. Doxorubicin induced toxicity is mediated through multiple interrelated mechanisms including excessive generation of reactive oxygen species, mitochondrial dysfunction, inflammatory signalling, disruption of calcium homeostasis and activation of apoptotic pathways. These mechanisms contribute to cardiomyocyte degeneration, renal tubular injury, altered organ function and systemic metabolic derangements (Kciuk *et al*., 2023).

Benazepril, a long-acting angiotensin-converting enzyme inhibitor, possesses established cardioprotective and renoprotective properties through modulation of the renin–angiotensin–aldosterone system and improvement of haemodynamic stability (Ford *et al*., 2023). Hesperidin, a naturally occurring citrus bioflavonoid, has attracted considerable interest because of its antioxidant, anti-inflammatory, cardioprotective, nephroprotective and membrane-stabilizing properties (Syahputra *et al*., 2022).

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Nevertheless, comparative information regarding its protective efficacy against doxorubicin-induced cardio-renal toxicity under a controlled experimental design remains limited. In view of the toxicological significance of doxorubicin and the potential protective role of hesperidin, the present study was undertaken to evaluate clinical manifestations, feed intake, body weight, organ index, haematological changes and serum biochemical alterations in doxorubicin induced cardio-renal toxicity in Wistar rats and to assess the ameliorative effects of hesperidin in comparison with benazepril.

Materials and Methods

Experimental Design

The experimental protocol was examined and approved by the Institutional Animal Ethics Committee (IAEC), College of Veterinary Science and Animal Husbandry, Kamdhenu University, Navsari, Gujarat (IAEC Protocol No.: 147-VCN-VPP-2025). The study was carried out on 40 Wistar rats, randomly allocated into five groups comprising eight animals each. Group I served as the normal control and received 0.5% carboxymethyl cellulose orally daily for 28 days. Group II was maintained as the doxorubicin treated toxic control and received doxorubicin intraperitoneally at the dose rate of 2.5 mg/kg body weight once weekly for four weeks. Group III received doxorubicin as above along with benazepril at 10 mg/kg body weight orally daily for 28 days. Groups IV and V received doxorubicin as above in combination with hesperidin administered orally daily at dose rates of 100 mg/kg and 200 mg/kg body weight, respectively, for 28 days. Animals were procured, acclimatized and maintained under standard laboratory conditions with appropriate feed and water throughout the experiment.

Clinical Observations, Feed Intake and Body Weight

All rats were examined twice daily during the treatment period for the appearance of clinical signs and behavioural abnormalities. Body weight and feed consumption were recorded weekly throughout the experimental period. Feed intake was calculated on a group basis after accounting for feed leftovers.

Blood Collection and Analysis

Following completion of the experimental period, about 1.0-1.5 mL of blood was collected from each rat through the retro-orbital plexus under mild anaesthesia. Samples collected in K_3EDTA tubes were used for haematological evaluation, while blood collected in plain vials was allowed to clot at room temperature for serum separation. Serum was separated by centrifugation at 10,000 g for 10 min and stored at –20°C until biochemical analysis.

Haematological examination was conducted using an automatic haematology analyser (Exigo EOS Vet, Sweden). Parameters evaluated included haemoglobin, packed cell volume, total erythrocyte count, total leukocyte count, mean corpuscular volume, mean corpuscular haemoglobin concentration, mean corpuscular haemoglobin, total platelet count, lymphocytes, neutrophils, monocytes, eosinophils, and basophils. Biochemical analysis of serum samples was performed using standard commercial assay kits on a semi-automatic biochemical analyser (Micro Lab RX-50V). The biochemical parameters included cholesterol, triglycerides, total protein, albumin, creatinine, blood urea nitrogen, lactate dehydrogenase.

Organ Index

At necropsy, the heart and kidneys were collected and weighed for determination of relative organ weight. Organ index was calculated to evaluate treatment related changes in organ mass in relation to body weight.

Statistical Analysis

Data were analysed statistically using appropriate tests after assessment of significance at $p \leq 0.05$. The results were expressed as mean ± standard error and intergroup comparisons were made to determine the effects of doxorubicin and the ameliorative responses produced by benazepril and hesperidin.

Results and Discussion

Clinical Manifestations

Animals of the control group remained clinically normal throughout the experimental period showing normal activity, grooming behaviour and absence of visible abnormalities. In contrast, rats treated with doxorubicin exhibited marked clinical signs of systemic toxicity, including diarrhoea, lethargy, reduced locomotor activity, scruffy fur, chromodacryorrhoea, red discolouration of urine and progressive deterioration in body condition. These manifestations were most prominent in the toxic control group. Rats receiving benazepril or hesperidin along with doxorubicin showed noticeable amelioration of these clinical abnormalities and the protective effect was more evident in the hesperidin treated groups particularly at the higher dose. These findings indicate that doxorubicin produced marked systemic toxicity while co-administration of benazepril and hesperidin reduced the severity of these adverse clinical effects. Similar clinical manifestations in doxorubicin treated rats, including lethargy, rough hair coat, reduced activity, diarrhoea and generalized weakness have been reported by Chaudhary *et al*. (2016) and Podyacheva *et al*. (2022).

Feed Consumption

The effect of doxorubicin and its amelioration by benazepril and hesperidin on feed intake is presented in Table 1. Feed consumption remained comparable among groups during the initial phase of the experiment. However, from the third week onward, a decline in feed intake became evident in

the doxorubicin treated group (87.37±12.32 g) and became significant by the end of the fourth week. At week 4, feed consumption in the doxorubicin treated group (50.81±14.65 g) was significantly lower than that of the control group (128.22±12.52 g). In contrast, both hesperidin treated groups (Group IV 110.12±8.38 g, Group V 115.56±9.21 g) showed comparatively better feed consumption and by the fourth week their values were significantly higher than doxorubicin treated group. The benazepril-treated group (90.57±10.34 g) showed moderate improvement and remained intermediate between control and doxorubicin groups.

Feed consumption is indicator of general well-being during repeated drug exposure. The decline observed in the doxorubicin treated group likely reflects anorexia, gastrointestinal intolerance and generalized systemic toxicity induced by the drug. The comparatively better feed intake maintained in hesperidin treated rats may be attributed to its antioxidant and tissue-protective properties. Similar reductions in appetite and feed intake in doxorubicin treated experimental animals have been reported by Chaudhary *et al*. (2016). The improvement observed with hesperidin is in agreement with the protective effects of natural antioxidants reported in toxicological models, including the findings of Abdel-Raheem and Abdel Ghany (2009).

Body Weight

The effect of doxorubicin and associated treatments on body weight is presented in Table 2. Body weight did not differ significantly among the experimental groups during the first three weeks of the study. However, by the end of the fourth week, the doxorubicin treated group (249.82±16.56 g) showed a significant reduction in body weight compared with the control group (349.20±28.44 g). The hesperidin treated groups (Group IV 286.97±21.90 g, Group V 308.73±16.74 g) exhibited comparatively better maintenance of terminal body weight, whereas the benazepril treated group (274.63±20.12 g) remained lower than the control.

Loss of body weight is an indicator of repeated toxicity and reflects the combined impact of reduced feed intake, altered metabolism and organ dysfunction. In the present study, the terminal reduction in body weight in the doxorubicin treated group appears to be associated with cumulative toxic effects developing during repeated exposure. The comparatively improved body weight in hesperidin treated groups suggests preservation of metabolic status and general health. Similar body weight reduction after doxorubicin administration has been documented by Chaudhary *et al*. (2016) and Podyacheva *et al*. (2022). The protective trend observed with hesperidin is comparable to previous reports where hesperidin improved body weight maintenance under toxic stress conditions (Sahu *et al*., 2013).

Relative Organ Weight (Organ Index)

The effect of doxorubicin and its amelioration by benazepril and hesperidin on organ index is presented in Table 3. Relative heart weight varied significantly among the groups.

Table 1: Average feed consumption values (g/week/animal) of different experimental groups recorded throughout the study period

Duration	Treatment groups (Mean ± SE)				
	Control	Group II	Group III	Group IV	Group V
Week 1	127.82±6.56	120.37±9.02	103.45±7.30	109.25±7.37	105.61±9.36
Week 2	102.21±10.03	97.89±10.94	113.26±6.85	99.82±8.99	115.04±7.14
Week 3	132.82^{b}±11.01	87.37^{a}±12.32	101.16^{ab}±5.49	109.25^{ab}±7.91	114.34^{ab}±5.72
Week 4	128.22^{b}±12.52	50.81^{a}±14.65	90.57^{ab}±10.34	110.12^{b}±8.38	115.56^{a}±9.21

Values with different superscripts between the groups differ significantly (p≤0.05).

Table 2: Weekly average body weight (g) of different experimental groups recorded throughout the study period

Duration	Treatment groups (Mean ± SE)				
	Control	Group II	Group III	Group IV	Group V
0 Day	263.27±31.59	268.55±29.18	260.55±16.3	260.82± 27.54	269.90±23.70
7 Day	284.28±29.52	277.68±20.63	261.72±28.66	270.57±29.73	276.70±18.67
14 Day	300.98±34.66	265.88±22.08	266.47±25.48	273.87±26.76	283.77±21.42
21 Day	329.83±30.95	261.08±20.94	267.85±16.06	276.97±21.28	290.95±17.37
28 Day	349.20^{b}±28.44	249.82^{a}±16.56	274.63^{a}±20.12	286.97^{ab}±21.90	308.73^{ab}±16.74

Values with different superscripts between the groups differ significantly (p≤0.05).

Table 3: Relative organ weight values (%) of heart and kidney following treatment of doxorubicin and hesperidin

Organs	Treatment groups (Mean ± SE)				
	Control	Group II	Group III	Group IV	Group V
Heart	0.34^{a}±0.01	0.47^{b}±0.04	0.41^{ab}±0.09	0.39^{ab}±0.05	0.36^{a}±0.01
Kidney	0.70^{a}±0.02	0.83^{b}±0.04	0.80^{ab}±0.05	0.79^{ab}±0.02	0.74^{ab}±0.01

Values with different superscripts between the groups differ significantly (p≤0.05).

The doxorubicin treated group showed a significant increase in relative heart weight (0.47 ± 0.04) compared with the control group (0.34 ± 0.01). This increase persisted in the benazepril treated group (0.41 ± 0.09) and the low dose (100 mg/kg) hesperidin group (0.39 ± 0.05), whereas the high-dose (200 mg/kg) hesperidin treated group (0.36 ± 0.01) remained comparable to the control. Relative kidney weight was also significantly increased in the doxorubicin treated group (0.83 ± 0.04) as compared with the control (0.70 ± 0.02), while the benazepril and hesperidin treated groups did not differ significantly from the control.

Relative organ weight is a sensitive indicator of drug induced organ involvement and often reflects tissue edema, congestion, inflammatory changes or degenerative alterations. The increase in relative heart weight observed in the doxorubicin treated group may be attributed to myocardial injury associated with congestion, inflammation and structural disorganization. Similarly, the increase in relative kidney weight suggests renal involvement, possibly due to vascular congestion, tubular injury or interstitial edema. The normalization of organ indices in the high dose (200 mg/kg) hesperidin group indicates effective protection against these pathological changes. Consistent with our findings, Swamy *et al*. (2012) reported changes in relative weight following doxorubicin exposure and Sahu *et al*. (2013) reported normalization trend in high dose (200 mg/kg) hesperidin group.

Haematological Parameters

The mean values of haematological parameters are presented in Table 4. Doxorubicin administration caused a significant ($p<0.01$) reduction in haemoglobin, haematocrit, total erythrocyte count, total leukocyte count and absolute lymphocyte count in Group II compared with the corresponding control values of Group I. Co-administration of hesperidin produced a dose-dependent improvement in these parameters. The high-dose hesperidin group V showed marked restoration of haemoglobin, haematocrit, total erythrocyte count, total leukocyte count and absolute lymphocyte count. The low-dose hesperidin group VI also showed improvement, with relatively lower values of these parameters than in high dose group V. The benazepril treated group III also showed partial recovery (TLC: 14.37 ± 0.79 × 10^3/µL; absolute lymphocyte count: 6.45 ± 0.69 × 10^3/µL). No significant differences were observed among the groups in MCV, MCH, MCHC, platelet count and absolute neutrophil, monocyte, eosinophil and basophil counts.

The reduction in haemoglobin, haematocrit and total erythrocyte count indicates anaemia induced by doxorubicin due to bone marrow suppression and impaired erythropoiesis. The concurrent decrease in total leukocyte count and absolute lymphocyte count reflects leukopenia and lymphopenia, suggesting immunosuppressive and myelotoxic effects of doxorubicin. Anthracycline induced suppression of haematopoietic activity is well documented and is considered one of the major dose limiting toxic effects of the drug. The amelioration observed in hesperidin treated groups attributed to its antioxidant, membrane stabilizing and cytoprotective properties. The greater efficacy of high dose (200 mg/kg) hesperidin suggests a dose dependent protective action. Similar reductions in erythrocytic and leukocytic parameters following doxorubicin administration have been reported by Donia *et al*. (2018) and Yakout *et al*. (2021). Protective effects of hesperidin against toxicant induced haematological alterations have also been described by Urkude *et al*. (2021) and Kondampati *et al*. (2024).

Table 4: Haematological parameters of different experimental groups recorded at end of the study period

Parameters	Treatment groups (Mean ± SE)				
	Control	Group II	Group III	Group IV	Group V
Hb (g/dL)	14.85^{b}±0.81	9.17^{a}±1.84	10.12^{a}±0.12	12.83^{b}±0.23	13.68^{b}±0.35
HCT (%)	39.82^{b}±2.12	25.58^{a}±4.98	30.47^{a}±1.27	32.52^{ab}±1.22	39.22^{b}±0.91
TEC (x10^6/µL)	7.64^{b}±0.43	4.76^{a}±0.92	5.4^{a}±0.38	6.51^{b}±0.24	6.70^{b}±0.44
MCV (fL)	55.13±1.11	53.97±1.44	56.15±1.28	55.9±3.89	53.33±1.92
MCH (pg)	21.85±1.37	19.07±0.49	19.18±0.31	20.68±1.05	20.42±0.79
MCHC (g/dL)	35.63±0.71	37.35±0.41	36.4±0.53	35.68±0.89	34.92±1.54
Platelets (10^5/µL)	7.68±0.44	7.39±0.49	7.40±0.27	7.48±0.94	7.88±0.37
TLC (x10^3/µL)	14.45^{b}±0.56	9.42^{a}±1.74	14.37^{b}±0.79	14.02^{b}±2.13	13.85^{b}±1.17
Abs. Lymphocytes (x10^3/µL)	9.28^{b}±0.94	4.98^{a}±0.93	6.45^{ab}±0.69	6.72^{ab}±1.34	7.8^{ab}±0.58
Abs. Neutrophils (x10^3/µL)	4.95±0.33	3.55±0.71	5.52±0.45	6.43±1.52	5.68±1.33
Abs. Monocyte (x10^3/µL)	1.05±0.12	0.85±0.25	0.95±0.15	0.87±0.18	0.80±0.07
Abs. Eosinophils (10^3/µL)	0.13±0.06	0.19±0.04	0.17±0.09	0.34±0.04	0.31±0.07
Abs. Basophils (10^3/µL)	0.0±0.0	0.0±0.0	0.0±0.0	0.0±0.0	0.0±0.0

Values with different superscripts between the groups differ significantly ($p\leq0.05$).

Serum Biochemical Parameters

The mean values of serum biochemical parameters are presented in Table 5. Doxorubicin administration produced a significant increase in serum cholesterol, creatinine and blood urea nitrogen as compared with the control group. Hesperidin treatment ameliorated these biochemical alterations in a dose dependent manner in group IV and V. High dose (200 mg/kg) hesperidin showed a stronger protective effect on renal biochemical parameters, particularly by maintaining serum creatinine values near control levels and significantly reducing blood urea nitrogen.

The increase in serum cholesterol in doxorubicin treated rats suggests disruption of lipid metabolism, which indicates altered hepatic and cardiac function. Elevated serum creatinine and blood urea nitrogen indicate impairment of renal function and reduced glomerular filtration. The better response in the high dose (200 mg/kg) hesperidin group indicates greater efficacy in limiting doxorubicin induced renal and cardiac injury. Improvement in these biochemical indices following hesperidin treatment may be attributed to its antioxidant, anti-inflammatory and organ-protective properties. The absence of significant alteration in triglycerides, total protein, albumin and lactate dehydrogenase suggests that these parameters were less sensitive under the present experimental conditions. Similar biochemical disturbances after doxorubicin administration have been reported by Soltani *et al*. (2021) and Arvi *et al*. (2025). Comparable ameliorative effects of hesperidin on serum biochemical alterations have been documented by Donia *et al*. (2018) and Alharbi *et al*. (2023).

Conclusion

The present findings revealed that the repeated administration of doxorubicin at 2.5 mg/kg b.wt. intraperitoneally once weekly for four weeks induced marked systemic toxicity in Wistar rats, as evidenced by clinical signs of diarrhoea, lethargy, reduced locomotor activity, scruffy fur, chromodacryorrhea and red discoloration of urine, along with reduced body weight, feed consumption with altered relative heart and kidney weights. Doxorubicin caused marked haematoxicity by altering haematological parameters that were ameliorated by benazepril and higher dose of hesperidin. Doxorubicin administration impaired renal function's parameters. These were ameliorated by benazepril and dose dependent hesperidin.

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Table 5: Serum biochemical parameters of different experimental groups recorded at end of the study period

Parameters	Treatment groups (Mean ± SE)				
	Control	Group II	Group III	Group IV	Group V
Cholesterol (mg/dL)	25^{a}±1.84	51.33^{b}±4.05	42.5^{b}±4.05	51^{b}±5.64	41^{b}±4.55
Triglycerides (mg/dL)	78.78±7.06	108.35±15.69	164.5±70.72	71.35±10.61	75.23±25.54
Total protein (g/dL)	6.80±0.49	6.31±0.61	6.57±0.50	6.51±0.29	6.65±0.23
Albumin (g/dL)	2.99±0.14	3.33±0.16	3.21±0.18	3.29±0.21	3.21±0.08
Creatinine (mg/dL)	0.25^{a}±0.04	0.54^{c}±0.08	0.46^{c}±0.03	0.42^{bc}±0.06	0.30^{ab}±0.06
BUN (mg/dL)	14.56^{a}±0.58	20.79^{b}±3.68	16.20^{ab}±0.65	14.95^{a}±0.64	14.80^{a}±0.57
LDH (U/L)	212.50±6.80	398.33±10.17	366.83±6.24	324.33±9.86	311.17±6.67

Values with different superscripts between the groups differ significantly (p≤0.05).

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