

Cardioprotective effect of boswellic acids against doxorubicin induced myocardial infarction in rats

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Abstract: The aim of the present study was to evaluate the cardioprotective activity of boswellic acids in doxorubicin (DOX) induced cardiotoxicity. DOX (2.5mg/kg) was used intraperitoneally in rats to induce cardiotoxicity in six divided doses every alternate day over a period of two weeks. Dexrazoxane (10:1) was used as a standard drug. Boswellic acids (250, 500 and 750 mg/kg) were orally administered to rats for 14 days. After 14 days, rats were sacrificed, and blood was withdrawn through cardiac puncture. The blood lipid profile and cardiac biomarkers including LDH, CK-MB, CPK, SGOT and troponin T were measured. The heart of rats was isolated for histopathological studies. Graphpad Prism was used for statistical analysis. There was a significant increase in the level of cardiac enzymes and complete lipid profile parameters in diseased group as compared to control group. Pre-treatment with boswellic acids decreased level of all the measured parameters and decreased the severity of myocardial damage as supported by histopathological studies. It was concluded that boswellic acids possess cardioprotective potential by lowering cardiac biomarkers and blood lipid profile. Thus, boswellic acids might act as cardioprotective agent against doxorubicin induced cardiotoxicity.

Keywords: Boswellic acids, cardiac biomarkers, cardioprotective, doxorubicin.

INTRODUCTION

In accordance with the study of the World Health Organization, the world's largest mortality rate is due to the cardiovascular diseases which account for 17.1 million deaths each year (Behrouzian *et al.*, 2020). In the past few years, the natural therapy has gained much attraction and attention for curing the cardiovascular and metabolic disorders as this therapy has fewer side effects. A study revealed that there is high occurrence of myocardial infarction in Islamic Republic of Pakistan with more than 30% of the inhabitants are being affected (> 45 years of age) by this disease (Meier *et al.*, 2019, Khan *et al.*, 2018).

Doxorubicin (Dox) induced cardiomyopathy accounts for 1.7% to 6.8% in overall prevalence and is much dependent on gross dose (Skubitz *et al.*, 2017). The insidious onset of Dox-induced cardiotoxicity is generally followed by a promptly exaggerated failure of biventricular and sudden death (Syrkin and Bartels, 2018). Doxorubicin induced cardiomyopathy includes characteristic signs and symptoms of any biventricular failure such as cardiomegaly, hepatomegaly, gallop rhythms, ankle oedema, shortness of breath, tachycardia, pleural effusion, distention in neck vein and congestive heart failure (Kelleni and Abdelbasset, 2018, Szmit *et al.*, 2017).

Boswellic acids, isolated from *Boswellia serrata*, are one of the basic, most vital and normally used constituents in conventional Unani and Ayurveda medicines, that have

been proven to be highly effective in curing many microbial infections, hormonal, inflammatory as well as gastrointestinal disorders (Niringiyumukiza *et al.*, 2019, Songbo *et al.*, 2019). It possesses antiseptic, analgesic, hepatoprotective, nephroprotective, anti-inflammatory, tranquilizing and expectorant effects (Geetha and Chakravarthula, 2018, Virshette *et al.*, 2020, Shah, 2019). Previous reports have confirmed that boswellic acids possess antioxidant effects which are confirmed by increased level of reduced glutathione so, Dox-induced oxidative stress may be protected by boswellic acids (Shaker *et al.*, 2018). Traditionally, in Ayurveda medicine boswellic acids were used as a cardioprotective agent (Songbo *et al.*, 2019). The aim of the present study was to investigate the cardioprotective effects of boswellic acids by observing the effects on cardiac biomarkers in doxorubicin induced cardiotoxicity.

MATERIALS AND METHODS

Drugs used

Normal saline, chloroform, formalin, and distilled water was obtained from the main chemical store, The University of Lahore, Lahore. Dexrazoxane was obtained from Children Hospital, Lahore. For the biochemical analysis of cardiac enzymes (SGOT, LDH, CK-Mb and CPT) and lipid profile (HDL, triglyceride, total cholesterol, LDL and VLDL), standard Merck diagnostic kits were purchased from Khursheed Rasheed Hospital, Lahore. Doxorubicin, obtained from Mesochem Technology (China), was reconstituted with 0.9% normal saline. Boswellic acids (97%) were purchased from Yuantai Biological Technology (China).

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Animals used

This study included 30 adults male Wistar rats weighing 200 ± 10 g. These animals were purchased from animal house of Faculty of Pharmacy, The University of Lahore and then kept for 12 hour light/dark cycle and had free access to food and water with constant temperature at $22 \pm 2^\circ\text{C}$ and humidity (65-70%). This study was conducted with the approval from Animal Ethical Research Committee of Faculty of Pharmacy (IREC-2019-140), The University of Lahore, Pakistan.

Study Design

After 10 days of acclimatization, rats were divided into six groups ($n=5$). The solution of boswellic acids was prepared by dissolving boswellic acids (50 g) in normal saline (100 ml). Cardiotoxicity was induced in rats by intraperitoneal injection of doxorubicin (2.5 mg/kg) dissolved in normal saline in six doses over 14 day period.

Group I, control group; received normal saline (2 ml/kg) orally. Group II, diseased group; received doxorubicin (2.5 mg/kg) by intraperitoneal injection. Group III, standard drug treated; dexrazoxane at ratio of 10:1 to doxorubicin was given intravenously after two hours of doxorubicin (2.5 mg/kg). Group IV, V and VI: boswellic acid treated groups and were administered 250 mg/kg, 500 mg/kg and 750 mg/kg boswellic acid respectively orally 2 hours after doxorubicin (2.5 mg/kg).

Collection of blood and heart tissue

All the tested animals were sacrificed on 15th day by decapitation and the blood samples of rats were collected separately into sterilized dry centrifuge tubes which allowed coagulating after half an hour at 37°C . The serum obtained after centrifugation was used in estimating lipid profiles and cardiac enzymes (lactate dehydrogenase (LDH), creatine phosphokinase total (CPT), creatine phosphokinase MB (CPK) and serum aspartate amino transferase (AST or SGOT) using standard kits and troponin T was measured by using ELISA technique.

Histopathological studies

The heart of rat was cut out and washed instantly with normal saline and then placed in 10% buffered solution of formalin in a container; 5 μm thick sections were cut and stained with eosin and haematoxylin. These sections were observed under a light microscope (Chen *et al.*, 2017).

STATISTICAL ANALYSIS

The data were expressed as mean \pm SEM. The data obtained from different groups were statistically analysed by one-way analysis of variance, followed by Tukey's multiple comparison tests using Graph Pad Prism version 5.0.1. $P \leq 0.05$ was considered statistically significant.

RESULTS

Effect of boswellic acids on creatinine phosphokinase (CPK)

The level of CPK was measured for control, diseased, standard drug and boswellic acids (250, 500 and 750 mg/kg) treated groups. It was observed that level of CPK was increased (305 ± 13.95) in diseased group as compared to control group (63 ± 1.00) and decreased (69.4 ± 0.9) significantly in boswellic acids (750 mg/kg) treated group as shown in table 1.

Effect of boswellic acids on creatine kinase-MB (CK-MB)

The level of CK-MB was measured for control, diseased, standard drug treated and boswellic acids (250, 500 and 750 mg/kg) treated groups. It was observed that level of CK-Mb has been prominently increased (181 ± 3.31) in diseased control group as compared to control group (13.8 ± 0.73) and decreased (18.4 ± 0.67) significantly in boswellic acids (750 mg/kg) treated group (table 2).

Effect of boswellic acids on lactate dehydrogenase (LDH)

The level of LDH was measured for control, diseased (Dox), standard drug treated, boswellic acids (250, 500 and 750 mg/kg) treated groups. It was observed that level of LDH was significantly increased (445 ± 4.42) in diseased group as compared to control group (168 ± 1.11) and decreased (186 ± 1.225) markedly in boswellic acids (750 mg/kg) treated group (table 3).

Effect of boswellic acids on SGOT

The level of SGOT was measured for control, diseased, standard drug treated, boswellic acids (250, 500 and 750 mg/kg) treated groups. It was observed that level of SGOT was significantly increased (104 ± 3.64) in diseased group as compared to control group and decreased (30.4 ± 0.748) markedly in boswellic acids (750 mg/kg) treated group (table 4).

Effect of boswellic acids on cholesterol

The level of cholesterol was measured for control, diseased (Dox), standard drug treated, boswellic acids (250, 500 and 750 mg/kg) treated groups. It was observed that level of cholesterol was noticeably increased (282.8 ± 5.74) in diseased (Dox) group as compared to control group (148.6 ± 0.81) and decreased (155.8 ± 1.15) markedly in boswellic acids (750 mg/kg) treated group (table 5).

Effect of boswellic acids on triglycerides

The level of triglycerides was measured for all groups. It was observed that level of triglycerides was increased (230.2 ± 2.41) in diseased (Dox) group as compared to control group (116.2 ± 0.66) and decreased (117 ± 1.00) markedly in boswellic acids (750mg/kg) treated group shown in table 5.

Table 1: Effect of boswellic acids on CPK

Groups	Control (ug/L)	Diseased (Dox) (ug/L)	Standard drug treated (ug/L)	Boswellic acids 250 mg/kg (ug/L)	Boswellic acids 500 mg/kg (ug/L)	Boswellic acids 750 mg/kg (ug/L)
Mean ± SEM	(63±1.00)	(305±13.95)*	(61.8±0.8)**	(175±1.94)**	(124±1.39)**	(69.4±0.9)**

Determination of CPK level of control, diseased, standard drug treated and boswellic acids (250mg/kg, 500 mg/kg, 750mg/kg) treated group of rats (* $P<0.05$; compared to the control group, ** $P<0.05$ compared to diseased (Dox) group; n=5) in doxorubicin induced cardiotoxic model.

Table 2: Effect of boswellic acids on CK-MB

Groups	Control (u/L)	Diseased (Dox) (u/L)	Standard drug treated (u/L)	Boswellic acids 250 mg/kg (u/L)	Boswellic acids 500 mg/kg (u/L)	Boswellic acids 750 mg/kg (u/L)
Mean ± SEM	(13.8±0.73)	(181±3.31)*	(14.4±0.87)**	(21.2±2.26)**	(31.8±0.86)**	(18.4±0.67)**

Determination of level of CK-Mb of Control, diseased (Dox), standard drug treated, boswellic acids (250 mg/kg, 500 mg/kg, 750 mg/kg) treated group of rats (* $P<0.05$; compared to the control group, ** $P<0.05$ compared to diseased group; n=5) in doxorubicin induced cardiotoxic model.

Table 3: Effect of boswellic acids on LDH

Groups	Control (u/L)	Diseased (Dox) (u/L)	Standard drug treated (u/L)	Boswellic acids 250 mg/kg (u/L)	Boswellic acids 500 mg/kg (u/L)	Boswellic acids 750 mg/kg (u/L)
Mean ± SEM	(168±1.11)	(445±4.42)*	(172±0.73)**	(317±3.10)**	(266±0.86)**	(186±1.225)**

Determination of level of LDH of control, diseased (Dox), standard drug treated, boswellic acids (250mg/kg, 500mg/kg, 750mg/kg) treated group of rats (* $P<0.05$; compared to the control group, ** $P<0.05$ compared to disease group; n=5) in doxorubicin induced cardiotoxic model

Table 4: Effect of boswellic acids on SGOT

Groups	Control (u/L)	Diseased (Dox) (u/L)	Standard drug treated (u/L)	Boswellic acids 250mg/kg (u/L)	Boswellic acids 500 mg/kg (u/L)	Boswellic acids 750mg/kg (u/L)
Mean ± SEM	(22.8±0.663)	(104±3.64)*	(25.2±0.663)**	(90±2.302)**	(53.4±0.812)**	(30.4±0.748)**

Determination of level of SGOT of control, diseased (Dox), standard drug treated, boswellic acids (250 mg/kg, 500 mg/kg, 750 mg/kg) treated group of rats (* $P<0.05$; compared to the control group, ** $P<0.05$ compared to diseased group; n=5) in doxorubicin induced cardiotoxic model

Table 5: Effect of boswellic acids on blood lipid profile

Groups	Cholesterol (mg/dl)	Triglycerides (mg/dl)	HDL (mg/dl)	LDL (mg/dl)	VLDL (mg/dl)
Control	148.6±0.81	116.2±0.66	67.8±1.98	85±0.31	24.2±0.80
Diseased	282.8±5.74*	230.2±2.41*	32.4±1.6*	153±3.15*	46±0.548*
Standard drug treated	147.8±0.58**	109.4±0.75**	72.2±0.86**	82.4±0.92**	22±0**
Boswellic acids treated (250mg/kg)	235±2.40**	177.4±2.64**	39.8±0.86**	133±1.22**	35.2±0.58**
Boswellic acids treated (500mg/kg)	205.2±1.28**	154.8±0.97**	49.4±0.92**	109±0.95**	30.8±0.20**
Boswellic acids treated (750mg/kg)	155.8±1.15**	117±1.00**	65.4±1.03**	86±0.58**	23.4±0.24**

Data have been presented as Mean ±SEM. Determination of level of cholesterol, triglycerides, HDL, LDL and VLDL in control, diseased (Dox-2.5mg/kg), standard drug treated, boswellic acids (250mg/kg, 500mg/kg, 750mg/kg) treated group of rats (* $P<0.05$; compared to the control group, ** $P<0.05$ compared to diseased group; n=5) in doxorubicin induced cardiotoxic model.

Table 6: Effect of boswellic acids on Troponin-T

Groups	Control (ng/ml)	Diseased (Dox) (ng/ml)	Standard drug treated (ng/ml)	Boswellic acids 250 mg/kg (ng/ml)	Boswellic acids 500 mg/kg (ng/ml)	Boswellic acids 750 mg/kg (ng/ml)
Mean ± SEM	(0.05±0.002)	(0.122±0.007)*	(0.055±0.001)**	(0.077±0.009)**	(0.067±0.001)**	(0.056±0.001)**

Determination of Troponin T level of control, diseased, standard drug treated, boswellic acids (250mg/kg, 500 mg/kg, 750mg/kg) treated group of rats (* $P < 0.05$; compared to the control group, ** $P < 0.05$ compared to diseased (Dox) group; n=5) in doxorubicin induced cardiotoxic model

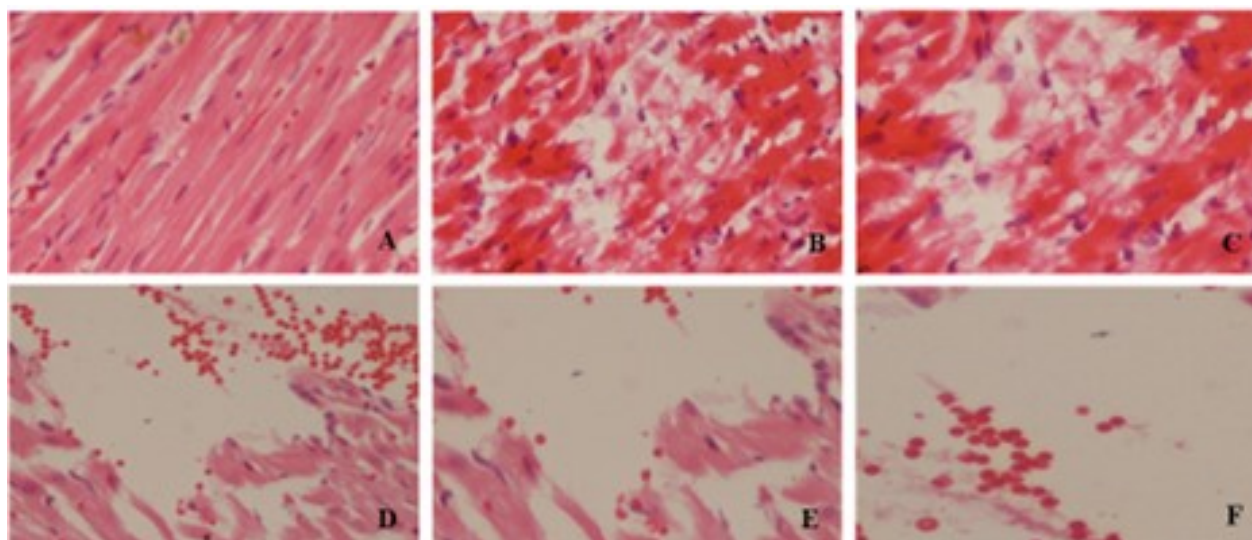


Fig. 1: (A) Intact normal cells with no tissue degeneration in control group, (B) In diseased group, coagulative necrosis can be recognized on haematoxylin and eosin (H&E) stained sections: ischemic myocytes typically showed the hyper eosinophilia that characterized early phases of coagulative necrosis, (C) Photomicrograph of standard drug treated (Dexrazoxane) indicating that nuclei, cytoplasm of myocytes and sinusoidal spaces were normal in appearance. (D) Subendocardial haemorrhage in boswellic acids (250mg/kg) treated group, (E) Healing myocardial infarct there was little bit inflammation and early fibroblasts without significant collagen deposition in boswellic acids (500mg/kg) treated group, (F) Photomicrograph of boswellic acids (750mg/kg) treated group showing almost normal cardiac parenchyma.

Effect of boswellic acids on LDL

The level of LDL was measured for control, diseased, standard drug treated, boswellic acids (250, 500 and 750 mg/kg) treated groups. It was observed that level of LDL was significantly increased (153±3.15) in diseased group as compared to Control group (85±0.31) and decreased (86±0.58) markedly in boswellic acids (750mg/kg) treated group (table 5).

Effect of boswellic acids on HDL

The level of HDL was measured for all six groups. It was observed that level of HDL was significantly decreased (32.4±1.6) in diseased group as compared to control group and increased (65.4±1.03) markedly in boswellic acids (750mg/kg) treated group (table 5).

Effect of boswellic acids on VLDL

The level of VLDL was measured for control, diseased (Dox), standard drug treated, boswellic acids (250, 500 and 750 mg/kg) treated groups. It was observed that level

of VLDL was increased significantly (46±0.548) in diseased (Dox) group as compared to control group (24.2±0.80) and decreased (23.4±0.24) markedly in boswellic acids (750 mg/ kg) treated group (table 5).

Effect of boswellic acids on Troponin T

Troponin T level was measured for control, diseased (Dox), standard drug treated, boswellic acids (250, 500, 750 mg/kg) treated groups. It was observed that level of troponin t was markedly increased (0.122±0.007) in diseased (Dox) group as compared to control group (0.05±0.002) and decreased (0.056±0.001) significantly in boswellic acids (750mg/kg) treated group as shown in table 6.

Histopathological Studies

The cardiac tissues were evaluated for histopathological studies. Diseased group showed necrosis of muscle fibres, inflammatory cell infiltration and oedema with fragmentation of muscle fibres as compared with the

control group. Treatment with boswellic acids (500 and 750 mg/kg) in doxorubicin treated rats showed moderate degree of oedema, necrosis and inflammatory cells as shown in fig. 1.

DISCUSSION

Imbalance in supply and demand of oxygen usually leads to myocardial infarction, that is frequently triggered by plaque rupture in coronary artery epicardium, with the formation of thrombus resulting in severe reduction of blood supply to myocardium (Beniwal *et al.*, 2018). Myocardial infarction results from any interruption in the blood supply to any part of the heart and leads to the death of the cardiac tissues (myocardial necrosis). In addition, increased migration of neutrophils to myocardial ischemic tissues contributes to the pathogenesis of myocardial injury (Enzmann *et al.*, 2018).

Doxorubicin is an anthracycline antibiotic, used extensively as chemotherapeutic agent in the treatment of bladder cancer, lymphomas, breast cancer and acute lymphocytic leukaemia (Oikonomou *et al.*, 2018). Although doxorubicin has become one of the most effective chemotherapeutic agent, it has been noted that its use is complicated by the development of heart failure (Henriksen, 2018). Clinical outcomes of doxorubicin are neutralized by its progressive cardiotoxicity which may yield a severe cardiomyopathy (Henriksen, 2018).

Boswellia is a moderate-sized flowering plant native to tropical regions of Africa and Asia. There are several known boswellia species; *B. serrata* or Indian frankincense is most commonly used for medicinal purposes. *B. serrata*, via its active boswellic acids, appears to exhibit potential anti-inflammatory, anti-asthmatic, anti-tussive, anti-tumor and anti-microbial properties (Iram *et al.*, 2017, Vuddanda *et al.*, 2016). The current study was focused on determining the cardioprotective effect of boswellic acids against doxorubicin-induced myocardial infarction in rats.

CPK is an enzyme found in body, mainly in the heart. Abnormal levels of CPK indicates myocarditis that leads to myocardial infarction (Koren *et al.*, 2019). In the present study, in diseased group, CPK level was enhanced that indicated myocardial impairment. While in boswellic acids (250mg/kg, 500mg/kg and 750mg/kg) treated groups, there was significant decline in CPK level. It depicts the cardioprotective potential of boswellic acids. At high doses of boswellic acids, the response was comparable with the standard group.

CK-MB is regarded as a standard diagnostic marker for measuring myocardial injury. Increased level of CK-MB in blood serum shows more chances of heart attack (Odum and Wakwe, 2017). In the present study, diseased group showed increased level of CK-MB levels. In

boswellic acids treated groups, the decreased concentrations of CK-MB justified its dose dependent cardio-protective response.

LDH was an important diagnostic measure for myocardial injury before the discovery of other biomarkers (Griffin *et al.*, 2020, Pudil *et al.*, 2020). This study highlighted that in diseased group, doxorubicin tended to increase the level of LDH in blood thus indicating heart attack or chronic cardiac failure. Boswellic acids at high dose (750 mg/kg) showed highly significant results and decreased the level of LDH.

SGOT was also measured to indicate the muscular breakdown of heart (Padulo *et al.*, 2018). In diseased group, SGOT level was high as compared to control and standard group. In all the treated groups, increasing dose trend of boswellic acids showed the cardioprotective response by decreasing SGOT levels in the blood.

There were marked increase in the levels of LDL, VLDL, triglycerides, and total cholesterol, while the HDL level in each group was decreased after administration of doxorubicin. While, the co-administration of boswellic acids with doxorubicin reduced the levels of LDL, VLDL, total cholesterol and triglycerides. The present results are comparable with the previous studies which indicated that boswellic acids significantly reduced the levels of triglyceride, total cholesterol, LDL and VLDL and showed increased level of HDL respectively (Mubarak *et al.*, 2018).

Troponin-t test is the most advanced tool for the early detection of heart attack. Troponin is released as a result of heart injury. Greater the level of troponin-t in the blood, more chances of heart attack or heart injury (Myburgh *et al.*, 2019, Nass *et al.*, 2019). Results showed that doxorubicin increased the Troponin-T levels. In boswellic acids treated groups (250 mg/kg, 500 mg/kg, 750mg/kg), Troponin-T levels were significantly decreased at high doses, thus, indicating boswellic acids as strong cardioprotective agent. These findings correlated with the previous studies (Milwidsky *et al.*, 2019).

The histopathological studies of heart from rats of all the groups were performed. The control group showed normal physiology of myocardium and no degeneration was found in the tissues and these results correlated with cardiac biomarkers in this study. In diseased group, it was clear and evident that necrosis occurred followed by tissue degeneration that showed signs of myocardial impairment. In boswellic acids treated group (boswellic acids 250 mg/kg), there was a change in morphology of heart and indicated injury but also showed a minor cardioprotective response, but this response was increased by increasing the concentration of boswellic acids in group 4 and 5 respectively.

The present study depicts that boswellic acids improved the serum cardiac enzymes and histopathological studies confirmed these findings. Low dose of boswellic acids (250 mg/kg) was described to prevent ulcer production in rats (Ali *et al.*, 2015). Another study verified the cardioprotective activity of boswellic acids in isoprenaline induced myocardial infarction model (Yu *et al.*, 2018).

Dexrazoxane used as standard drug in current study, is an iron chelator and possibly shows cardio protection by interrupting iron metabolism. The iron is supposed to produce additional reactive oxygen species which results in DNA impairment by increased lipid peroxidation. In the current study, boswellic acids (750 mg/kg) depict almost similar effects as that of the standard drug. The mechanism of boswellic acids may be proposed similar as that of dexrazoxane (Liesse *et al.*, 2018, Hasinoff *et al.*, 2020).

CONCLUSION

It is concluded that boswellic acids possesses cardioprotective potential by restoring cardiac biomarkers and improving blood lipids profile. There is a great need of more clinical research in-order to attain full benefits and hypothetical mechanism of cardio-protection from this phytochemical.

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