Cardioprotective effect of ellagic acid on doxorubicin induced cardiotoxicity in wistar rats

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Abstract

Background/Aim: The objective of the study was to evaluate the cardioprotective activity of ellagic acid in doxorubicin induced cardiotoxicity. Methods: Male wistar rats (180–220 g) were divided into four groups: vehicle control, doxorubicin control, ellagic acid (100 mg/kg) and ellagic acid (200 mg/kg). Doxorubicin was administered to all the groups except vehicle control at a dose of 3.75 mg/kg at week 2, 3, 4, 5 to make a cumulative dose of 3.75 mg/kg. Ellagic acid was administered to the respective group of animals at a dose of 100 mg/kg 200 mg/kg, respectively once daily orally for 6 weeks. On the last day of the study, blood was collected by retro-orbital puncture and LDH and CK-MB were estimated. The animals were cannulated and the ECG and hemodynamic parameters were recorded. The animals were then sacrificed and histology of heart was performed.

Results: Doxorubicin showed cardiotoxicity manifested by changes in serum marker enzymes, ECG and hemodynamic parameters which was further confirmed by histology of heart. This doxorubicin induced changes were attenuated by treatment with ellagic acid (200 mg/kg).

Conclusion: It has been concluded that ellagic acid (200 mg/kg) treatment for 6 weeks protects the heart of rats in doxorubicin induced cardiotoxicity.

Keywords: ellagic acid; cardioprotective; doxorubicin

1. Introduction

Doxorubicin is an anticancer drug which belongs to anthracycline antibiotics and is being used widely for treatment of various hematological and solid tumor malignancies including breast cancer, leukemia, and sarcomas.1,2 However, its clinical uses are limited by dose-dependent side effect of cardiotoxicity, which may lead to irreversible cardiomyopathy and eventually heart failure.3,4 The incidence of doxorubicin-related cardiotoxicity increases sharply above a cumulative dose of 550 mg/m² body surface area. So, the maximum recommended cumulative dose of Doxorubicin was tentatively set at 500 or 450 mg/square meters.3 Doxorubicin induced cardiotoxicity is mediated through different mechanisms including free radical production, calcium overloading, mitochondrial dysfunction and peroxynitrite formation have been proposed.5–8 Doxorubicin is enzymatically reduced to its semiquinone radical.9 This Doxorubicin semiquinone radical directly transfers its electron to molecular oxygen, generating a superoxide radical and hydrogen peroxide.10 As reactive oxygen species (ROS) play important roles in Doxorubicin-induced toxicity. Many compounds with antioxidant properties have been examined as potential therapeutic and/or
protective agents. Among these compounds were cranberry,\textsuperscript{11} p-coumaric acid,\textsuperscript{12} Withania somnifera,\textsuperscript{13} Lycium barbarum,\textsuperscript{14} Catechin\textsuperscript{15} and carvedilol.\textsuperscript{16}

In recent years, polyphenols have attracted considerable attention as agents that protect cells or molecules from oxidative myocardial injury. Ellagic acid is polyphenolic phytonutrient found in wide varieties of berries and nuts, and it has received particular attention because of its extensive array of biological properties. Previous studies indicated that ellagic acid showed free radical scavenging action, chemopreventive, antiinflammatory, anti-cataractogenetic, cardioprotective, gastroprotective, ulcer healing, antifibrotic, antidiabetic, hypolipidemic, antiatherosclerotic and estrogenic/antiestrogenic properties.\textsuperscript{17–30}

Polyphenols are excellent cardioprotectants. Hence, we hypothesized that ellagic acid may have a cardioprotective effect. The objective of the present study was designed to investigate the protective effect of the oral pretreatment of ellagic acid on experimentally induced myocardial infarction in Wistar rats. This study also attempted to explain the possible mechanism of the ellagic acid, by studying the electro cardiological, hemodynamic, biochemical changes in doxorubicin induced cardiotoxicity.

2. Methods

2.1. Drugs and chemicals

Ellagic acid and doxorubicin were purchased from Sigma Chemical Co., St. Louis MO, USA, urethane (Hi-Media Laboratories Mumbai), anesthetic ether (Narson Pharma), formaldehyde solution (35% formalin) (Merck Ltd), heparin (Gland Pharma Ltd) and normal saline (Baxter Ltd) were purchased from respective vendors. All other chemicals used in this study were of analytical grade.

2.2. Experimental animals

All the experiments were carried out with male Wistar rats aged 3–4 months, weighing 180–220 g, purchased from the National Institute of Bioscience, Pune, They were housed in polypropylene cages (47 × 34 × 20 cm) lined with husk, renewed every 24 hours under a 12-hour light/dark cycle at around 22°C with 50% humidity. The rats had free access to water. The rats were fed on a standard pellet diet (Chakan oil mills, Pune, Maharashtra, India) once a day. The experimental protocol was approved by the Institutional Animal Ethics Committee (IAEC) constituted in accordance with the rules and guidelines of the Committee for the Purpose of Control and Supervision on Experimental Animals (CPCSEA), India.

2.3. Experimental design and protocol

A total of 24 animals were randomly divided into four groups comprising of six animals per group.

Group I: control group, received 2% gum acacia as a vehicle for 42 days and normal saline (i.p) on day 14, 21, 28 and 35.

Group II: received Doxorubicin in normal saline (3.750 mg/kg) i.p on day 14, 21, 28 and 35 to reach total cumulative dose (15 mg/kg).

Group III: received ellagic acid (100 mg/kg p.o) in 2% gum acacia for 42 days and then doxorubicin in normal saline (3.750 mg/kg) i.p on day 14, 21, 28 and 35 to reach total cumulative dose (15 mg/kg).

Group IV: received ellagic acid (200 mg/kg p.o) in 2% gum acacia for 42 days and then doxorubicin in normal saline (3.750 mg/kg) i.p on day 14, 21, 28 and 35 to reach total cumulative dose (15 mg/kg).

2.4. Serum parameters

One week after the last i.p injection of doxorubicin (day 42, 168 hours from last dose of doxorubicin), blood was collected from the retro-orbital plexus of each rat under mild ether anesthesia (Narson Pharma, India) for determination of biochemical parameters. Serum was separated in a cryocentrifuge (Eppendorf, India) at 4°C at 7000 rpm for 15 minutes and lactate dehydrogenase (LDH), creatine phosphokinase-MB isoenzyme (CK-MB) were measured by using standard kits according to the manufacturer’s instruction manual (Merck Specialities Pvt. Ltd. India) using an autoanalyzer (Nihon Kohden, Japan).

2.5. Electrocardiogram

ECG was recorded before beginning of treatment and 1 week after the last doxorubicin injection, the electrocardiograph patterns were recorded by an eight-channel PowerLab (ADInstruments, Bella Vista, New South Wales, Australia) running LabChart Pro 7 software (ADInstruments). The types of alterations (QT interval, ST-segment elevation and QRS complex) in the experimental rats were recorded.

2.6. Hemodynamic parameters

One week after the last i.p doxorubicin injection animals were anesthetized by urethane (1.25 g/kg). The right carotid artery of each rat was cannulated for the measurement of heart rate (HR), systolic blood pressure (SBP), diastolic blood pressure (DBP) and mean arterial blood pressure (MABP). The cannula was filled with heparinised saline and connected to pressure transducer. The hemodynamic parameters were recorded by an eight-channel PowerLab (ADInstruments) running LabChart Pro 7 software (ADInstruments). Left ventricular systolic pressure was measured by means of a Millar mikro-tip transducer catheter inserted into the left ventricle via the right carotid artery and connected to a BM 614R2 amplifier (ADInstruments). dp/dt\textsubscript{Max}, dp/dt\textsubscript{Min} and LVSP signals were obtained from primary signals by means of an acquisition data system (ADInstruments) All the above signals were continuously recorded by means of the acquisition data system indicated above.

After recording of hemodynamic parameters, the animals were euthanized, and the heart was removed. A section of heart was homogenized in Tris-HCl buffer and
myeloperoxidase, glutathione, superoxide dismutase and catalase were determined.\textsuperscript{11} The other section was placed in 10% formalin solution for histopathology.

2.7. Antioxidant parameters

2.7.1. Measurement of TBARS

The Thiobarbituric acid-reactive substance was measured as a marker of lipid peroxidation in the pancreas. The homogenized pancreatic tissue was added to 1.5 ml of 8.1% sodium dodecyl sulphate, 1.5 ml of 20% acetate buffer (pH 3.5) and 1.5 ml of 0.8% TBA (Thiobarbituric acid) solution. The mixture was heated at 95°C for 1 hour. After cooling, 5 ml of n-butanol-pyridine (14:1) was added for extraction and the absorbance of n-butanol-pyridine layer at 532 nm (Schimadzu UV-Vis 1700) was measured for determination of TBA reactive substance.\textsuperscript{11}

2.7.2. Determination of glutathione

An aliquot of pancreatic tissue homogenate supernatant (0.4 ml) was added to dark polyethylene tube containing 1.6 ml of 0.4 M Tris – EDTA buffer, pH 8.9. After vortex-mixing, 40 μl of 10 mM dithiobisnitrobenzoic acid in methanol was added. The samples were vortex-mixed again and the absorbance at 412 nm was read after 5 minutes (Schimadzu UV-Vis 1700). The values of unknown samples were drawn from a standard curve plotted by assaying different known concentrations of glutathione (GSH). The amount of GSH was expressed as μmol/g of protein.\textsuperscript{11}

2.7.3. Measurement of superoxide dismutase (SOD)

Total SOD activity was measured by determining the ability to inhibit the auto-oxidation of pyrogallol. The rate of auto-oxidation was determined by measuring increases in the absorbance at 420 nm. Reaction mixture containing 0.2 mM pyrogallol in 50 mM Tris-cacodylic acid buffer (pH 8.5) and 1 mM diethylene triamine penta acetic acid was incubated for 90 seconds at 25°C. One unit of SOD activity is defined as the amount of the enzyme required to inhibit the rate of pyrogallol auto-oxidation by 50%.\textsuperscript{11}

2.7.4. Measurement of catalase (CAT)

CAT activity was assayed with hydrogen peroxide as the substrate using a method based on the direct measurement of H₂O₂ decomposition. CAT activity was determined by measuring the exponential disappearance of H₂O₂ at 240 nm and expressed as units/mg of protein as described by Aebi. The final volume of each enzymatic assay was 3 ml of substrate and 20 μl of the supernatant of pancreatic tissue homogenate. The assay was performed at 25°C and measured at 240 nm. Enzyme activity was expressed as units per gram of protein, and one unit of CAT activity represented 1 mmol H₂O₂ decomposed per minute.\textsuperscript{11}

2.8. Histopathology

The organ specimens were subjected to dehydration with xylene (1 hour each) and alcohol of 70%, 90% and 100% strength each for 2 hours. The infiltration and impregnation was carried out by treatment with paraffin wax twice for each time for one hour. Paraffin wax was used to prepare paraffin L molds. Specimens were cut into sections of 3–5 mm thickness and stained with hematoxylin and eosin. The sections were mounted by diestrene phthalate xylene. The parameters of histopathology assessment of heart sections were hyperemia, cellular infiltration and necrosis. The grading system used for assessment of parameters was (−: absence of change; +: 0–25% area shows changes; ++: 25–50% area shows changes; +++: 50 -75%; ++++:75–100% area shows changes).

2.9. Statistical analysis

Data were expressed as the mean ± SEM of six values. Statistical analysis was carried out by one-way ANOVA followed by Tukey's multiple comparison test using GraphPad Prism 5.00 for Windows (GraphPad Software Inc., La Jolla, CA, USA). The p value was considered significant when $p < 0.05$.

3. Result

3.1. Heart weight to body weight ratio

The doxorubicin treated rats showed a significant decrease in the heart weight to body weight ratio ($p < 0.001$) when compared to vehicle control group. On oral treatment with ellagic acid at 200 mg/kg for a period of 42 days significantly increased the heart weight to body weight ratio ($p < 0.05$) when compared to doxorubicin group, while treatment with ellagic acid at 100 mg/kg for a period of 42 days non-significantly increased the heart weight to body weight ratio when compared to doxorubicin group (Fig. 1).
3.2. Evaluation of serum parameters

Table 1 shows the effect of ellagic acid on biochemical parameters of the vehicle control and experimental rats. The doxorubicin treated rats showed a significant ($p < 0.001$) increase in the levels of serum creatine kinase and lactate dehydrogenase in the serum, when compared to the vehicle control rats. The oral treatment with ellagic acid at 200 mg/kg for a period of 42 days significantly ($p < 0.001$ and $p < 0.01$) decreased the elevated level of serum creatine kinase and lactate dehydrogenase when compared to doxorubicin group, while oral pretreatment with ellagic acid at 100 mg/kg for a period of 42 days non-significantly decrease the elevated level of creatine kinase and lactate dehydrogenase in serum when compared to doxorubicin group.

3.3. Evaluation of ECG parameters

Table 2 shows the effect of ellagic acid on the electrocardiographic changes of the vehicle control and experimental rats. The doxorubicin treated rats showed a significant ($p < 0.001$ and $p < 0.01$) increase in QT interval, ST segment along with a non significant increase in QRS complex as compared to the vehicle control group. The oral pretreatment with ellagic acid at 200 mg/kg for a period of 42 days showed significant ($p < 0.01$) decrease in QT interval and ST segment along with non significant decrease in QRS complex when compared to doxorubicin treated rats, while oral pretreatment with ellagic acid 100 mg/kg for a period of 42 days non-significantly decrease in QT, ST interval and QRS complex when compared to doxorubicin group.

3.4. Evaluation of hemodynamic parameters

Table 3 shows the effect of ellagic acid on the arterial blood pressure of the vehicle control and experimental rats. The doxorubicin treated rats showed a significant decreases in the systolic ($p < 0.01$), diastolic ($p < 0.05$) and mean arterial blood pressure ($p < 0.01$) as compared to the vehicle control group. Oral treatment with ellagic acid at 200 mg/kg for a period of 42 days showed a significant increase in the systolic and mean arterial blood pressure ($p < 0.05$) along with non-significant increase in diastolic blood pressure as compared to the doxorubicin group, while treatment with ellagic acid at 100 mg/kg for a period of 42 days non-significantly increased in the systolic, diastolic and mean arterial blood pressure as compared to the doxorubicin group. We observed a non significant decrease in the heart rate of the doxorubicin group. The oral pretreatment of ellagic acid (100 and 200 mg/kg) non-significantly increased in reduced heart rate when compared to the doxorubicin group. However, we also observed dp/dt_max, dp/dt_min and LVSP (Table 3). The doxorubicin treated rats showed significant ($p < 0.05$) decrease in the dp/dt_max, dp/dt_min and LVSP when compared to vehicle control group. Oral treatment with ellagic acid at 200 mg/kg for a period of 42 days non-significantly increased in dp/dt_max, dp/dt_min and non-significantly ($p < 0.05$) increase LVSP when compared to the doxorubicin group, while pre-treatment with ellagic acid at 100 mg/kg for a period of 42 days non-significantly increased in dp/dt_max, dp/dt_min and LVSP when compared to the doxorubicin group.

3.5. Antioxidant parameters

3.5.1. Malondialdehyde (MDA)

There was a significant increase ($p < 0.05$) in the lipid peroxidation in the doxorubicin group, which was evident with the increase in malondialdehyde levels (MDA). Treatment with ellagic acid (100 and 200 mg/kg) significantly ($p < 0.05$ and $p < 0.01$, respectively) decreased this elevated malondialdehyde (Table 4).

3.5.2. Glutathione

There was a significant decrease ($p < 0.05$) in the glutathione levels in the doxorubicin group when compared to the vehicle control rats. However, treatment with ellagic acid (100 mg/kg) non-significantly increased glutathione levels as compared to the doxorubicin group.

<table>
<thead>
<tr>
<th>Treatment Groups Parameters</th>
<th>Vehicle Control</th>
<th>Doxorubicin 100 mg/kg</th>
<th>Doxorubicin 200 mg/kg</th>
</tr>
</thead>
<tbody>
<tr>
<td>HR</td>
<td>373 ± 16</td>
<td>326 ± 11</td>
<td>331 ± 18</td>
</tr>
<tr>
<td>SBP</td>
<td>122 ± 4.5</td>
<td>90 ± 5.4</td>
<td>98 ± 6.7</td>
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<tr>
<td>DBP</td>
<td>86 ± 6.4</td>
<td>62 ± 5.9*</td>
<td>69 ± 5.9</td>
</tr>
<tr>
<td>MABP</td>
<td>106 ± 4.9</td>
<td>79 ± 5.6*</td>
<td>86 ± 5.9</td>
</tr>
<tr>
<td>dp/dt_max</td>
<td>2808 ± 192</td>
<td>1232 ± 101*</td>
<td>1290 ± 65</td>
</tr>
<tr>
<td>dp/dt_min</td>
<td>684 ± 65</td>
<td>451 ± 26*</td>
<td>506 ± 47</td>
</tr>
<tr>
<td>LVSP</td>
<td>116 ± 4.2</td>
<td>93 ± 4.0*</td>
<td>99 ± 5.0</td>
</tr>
</tbody>
</table>

Values are expressed as mean ± SEM ($n = 6$), one-way ANOVA followed by Tukey’s multiple comparison test. *$p < 0.05$, **$p < 0.01$ and ***$p < 0.001$ as compared to vehicle control group.
and 200 mg/kg) significantly increased (p < 0.05 and p < 0.01, respectively) these levels (Table 4).

3.5.3. Superoxide dismutase
There was a significant decrease (p < 0.05) in the superoxide dismutase levels in the doxorubicin group when compared to the vehicle control rats. However, treatment with ellagic acid significantly increased (p < 0.01) these levels (Table 4), which validates the antioxidant property of ellagic acid.

3.5.4. Catalase
There was a significant decrease (p < 0.05) in the catalase levels in the doxorubicin group when compared to the vehicle control rats. However, treatment with ellagic acid significantly increased (p < 0.01) these levels (Table 4), which validates the antioxidant property of ellagic acid.

3.6. Histopathology

**Fig. 2** illustrates the section of heart tissue in vehicle control rats (A), rats that received Doxorubicin only (B), rats that received Doxorubicin + EA (100 mg/kg) (C) and rats that received Doxorubicin + EA (200 mg/kg) The histopathology of the heart of the vehicle control group showed absence of hyperemia, cellular infiltration and necrosis (graded as − : absence of changes). Doxorubicin administration in the doxorubicin group showed hyperemia (+++), cellular infiltration (++++) and necrosis (++++) which means that hyperemia occurred in 25−50% area of the rat heart, cellular infiltration and necrosis occurred in a 75−100% area of heart and Cellular infiltration and necrosis in large areas of the heart confirmed cardiotoxicity in rats. On the other hand, hyperaemia(+), cellular infiltration(++) and necrosis(+++) were observed in a area of the heart (+, 0−25%; ++,25-50%; ++++,50-75%) in Doxorubicin + EA (200 mg/kg), while hyperemia (++), cellular infiltration (+++) and necrosis (+++) were observed in area of heart (+++,25-50%; ++++,50-75%; ++++++,75-100%) in Doxorubicin + EA (100 mg/kg). The results of histopathological analysis thus indicated that the rat heart was partially protected by pre-treatment with in EA (200 mg/kg) against doxorubicin-induced cardiotoxicity.

### 4. Discussion

The present study deals with the effect of ellagic acid in doxorubicin induced cardiotoxicity. Doxorubicin has been reported to cause cardiomyopathy in various animal species.20-23 Doxorubicin induced cardiotoxicity and oxidative stress has been confirmed in many experimental models. There is a prominent role of ROS including hydroxyl radical in doxorubicin induced cardiotoxicity. Doxorubicin is converted in the cardiac tissue into its semiquinone form, which is a toxic, short lived metabolite that interacts with molecular oxygen and initiates a cascade of reaction leading to ROS generation.24 The other reported mechanism of doxorubicin induced stress is the formation of an anthracycline-iron (Fe2+) free radical complex.25 The latter reacts with hydrogen peroxide to produce (OH−) radical. ROS react with lipids, protein and other cellular constituents causing damage to mitochondria and cell membranes of the heart muscle cells.26

The cardiac biomarker enzymes CK-MB and LDH are extensively used in the clinical practice as markers for the diagnosis of cardiac toxicity. Doxorubicin induces marked cardiotoxicity which was demonstrated by increase in CK-MB and LDH activities. Treatment with EA significantly prevented these increases and reversed doxorubicin induced hypotension and bradycardia. The magnitude of CK-MB and LDH activities in blood after myocardial injury reflects the extend of damage in its musculature.25 This was further confirmed by the histopathological changes in the heart including the fibrosis, apoptosis, loss of striation and inflammatory cells.

Treatment with doxorubicin resulted not only in mechanical dysfunction of the heart but also in inhomogeneity of ventricular depolarisation and repolarisation reflected by the occurrence of changes in the ECG. The observed ECG changes included prolongation of the ST segment, QRS intervals and QT interval. The cardiac dysfunction was also manifested by ECG changes, altered plasma levels of cardiac injury markers and histopathological changes in cardiac muscle along with decreased LVSP and decreased max and min dp/dt.26 Prolonged administration of doxorubicin caused decrease in heart rate, these result was consistent with earlier studies where it was hypothesized that reactive oxygen species generation may cause disturbance in calcium homeostasis. This could lead to reduction in heart rate because decrease in intracellular calcium induced reduced excitability of pacemaker cells in the SA node and other cells in the cardiac conducting system. Doxorubicin is an inhibitor of both systolic and diastolic cardiac function. Furthermore, its metabolite was more potent inhibitor than doxorubicin on the ion

### Table 4

<table>
<thead>
<tr>
<th>Treatment Groups Parameters</th>
<th>Vehicle Control</th>
<th>Doxorubicin</th>
<th>EA 100 mg/kg</th>
<th>EA 200 mg/kg</th>
</tr>
</thead>
<tbody>
<tr>
<td>MDA (nmol/g of protein)</td>
<td>37.4 ± 1.6</td>
<td>127.2 ± 3.12</td>
<td>83.1 ± 1.8</td>
<td>44.35 ± 2.6*</td>
</tr>
<tr>
<td>GSH (µmol/g of protein)</td>
<td>4.54 ± 0.25</td>
<td>1.52 ± 0.08</td>
<td>2.94 ± 0.62*</td>
<td>3.48 ± 0.12**</td>
</tr>
<tr>
<td>SOD (U/mg protein)</td>
<td>34.52 ± 1.4</td>
<td>15.52 ± 2.9</td>
<td>21.32 ± 1.42**</td>
<td>25.36 ± 1.58**</td>
</tr>
<tr>
<td>Catalase (U/mg protein)</td>
<td>8.26 ± 0.24</td>
<td>2.42 ± 0.62*</td>
<td>5.38 ± 0.36**</td>
<td>6.22 ± 0.48**</td>
</tr>
</tbody>
</table>

Values are expressed as mean ± SEM (n = 6), one-way ANOVA followed by Tukey's multiple comparison test. * p < 0.05, b p < 0.01 and ** p < 0.001 as compared to vehicle control group. * p < 0.05 and **p < 0.01 as compared to doxorubicin group.
pumps. Moreover, doxorubicin abolished the calcium loading activity of cardiac sarcoplasmic reticulum vesicle. Hence, LVSP, dp/dt max and dp/dt min are the direct indicators of cardiac systolic and diastolic function. In the present study, treatment with EA significantly attenuated the ST interval prolongation which shows that the cardiomyocyte injury was attenuated and the left ventricular function was preserved. Treatment with EA significantly reversed the LVSP which indicate that the cardiac function increased significantly. However, there was no significant difference observed with EA on max dp/dt and min dp/dt, which indicate that the heart rate was not affected.

Doxorubicin also caused a significant decrease in heart weight and heart body weight ration which indicate loss of myofibrils and myocardial necrosis. This is in line with the previous findings. Reduction of body weight, debilitation and death associated with multiple, long administration of DOX in experimental animals, are considered multifactorial. These are the results of direct toxic effects on intestinal mucosa appearing as mucositis, as well as additional indirect action on the gastrointestinal tract arising from reduced food intake causing a decrease in secretion of enteral hormones and resulting in decreased trophic effects to the mucosa. This suggestion is in accordance with the histopathological observations which revealed myocardial coagulation necrosis with fibrosis, vascular congestion as well as mononuclear infiltration. Treatment with EA decreased these necrosis, coagulation and fibrosis which further confirm the cardioprotective effect of EA.

Clinical and experimental investigations also suggested that increased oxidative stress plays a role in cardiomyopathy in heart failure associated with doxorubicin. There was a significant increase in the MDA, decrease in the GSH, CAT and SOD following doxorubicin administration when compared to vehicle control group. This clearly indicate the oxidative stress on the heart treated with doxorubicin. The observed GSH deficiency is due to GSH consumption in the interactions of DOX-induced free radicals with bio-membrane and the subsequent lipid peroxidation. Our studies observe the increased GSH, SOD and catalyse, which is because of the antioxidant property of ellagic acid which has inhibited the oxidative process in the heart.

5. Conclusion

In the present study, EA (200 mg/kg) is proven to have a cardioprotective effect in doxorubicin induced cardiotoxicity. This study suggests a possible usefulness of EA as a cardioprotective agent contributing to a safer use of doxorubicin.
in patient subjected to chemotherapy. However, cardioprotective effect was observed only in the higher dose of EA. Further dose response and bioavailability studies are needed to prove the efficacy of EA as a cardioprotective drug.

Conflicts of interest

We declare that we have no conflicts of interest.

Acknowledgments

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References


