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The Cardioprotective Effects Of Bromelain On Wistar Rat Myocardial Cells Induced By Doxorubicin: An Evaluation Based On Troponin T And Troponin I

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ABSTRACT

Globally, 2.3 million women are diagnosed with breast cancer annually, leading to an estimated 670,000 deaths. Doxorubicin (DOX), one of the anthracycline chemotherapeutic agents widely used in various malignancies including breast cancer, poses a significant therapeutic dilemma due to its association with doxorubicin-induced cardiotoxicity (DIC). Bromelain, an extract from Ananas comosus, has gained attention as a plant-derived compound with cardioprotective potential, primarily due to its potent antioxidant activity. This study aims to evaluate the cardioprotective effect of bromelain in DIC in Wistar rats using troponin T (cTnT) and I (cTnI) as cardiac biomarkers.

Fifteen Wistar rats (150–200 g) were randomized into three groups: (P1) Normal, (P2) DOX (15 mg/kg, i.p) and (P3) DOX (15 mg/kg, i.p) + Br (40 mg/kg, p.o). After 14 days, blood was collected for cTnT and cTnI measurement. Data were analyzed using one-way ANOVA, and significant outcomes were examined with Bonferroni post hoc comparisons.

cTnT and cTnI were significantly increased in the DOX group ($p<0.001$). Post-hoc Bonferroni analysis confirmed a significant reduction in serum cTnT ($p = 0.05$; 95%CI, −0.0005-0.348 ng/mL) and cTnI ($p = 0.022$; 95%CI, 0.028-0.384 ng/mL) in the P3 group.

Bromelain exerts a cardioprotective effect on the myocardial cells of doxorubicin-induced Wistar rats.

KEYWORDS: Bromelain, doxorubicin-induced cardiotoxicity, cardioprotective, troponin, Wistar rats.

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INTRODUCTION

Based on the Global Burden of Cancer (GLOBOCAN) data in 2022, it is estimated that 2.3 million (11.6%) women were diagnosed with breast cancer, resulting in 670,000 deaths. Meanwhile, in Indonesia in 2022, the incidence of breast cancer was statistically recorded at 66,300 cases (6.73%), causing 22,600 (7.17%) deaths (Bray, F, 2022). The number of breast cancer patients recorded at Dr. Soetomo General Hospital from 2021 to 2022 increased from 118 cases to 409 new cases (Muh. Zul A et al., 2024).

The effectiveness of doxorubicin (DOX) has been proven in cancer treatment, but this chemotherapeutic agent can have side effects, particularly cardiotoxic effects. The mechanism of doxorubicin-induced cardiotoxicity (DIC) is still not fully understood. The widely accepted theory is that this drug has the ability to cause DNA damage, free radical formation, cell apoptosis, mitochondrial dysfunction, calcium (Ca^{2+}) overload, increased inflammatory mediators, and autophagic flux disorder (Rawat et al., 2021; Sebayang, 2021; Renu et al., 2018). A previous cohort study showed that among 2625 cancers treated with doxorubicin, 9% of patients experienced cardiotoxicity with a mean follow-up time of 5.2 years (98% of which occurred within the first year) (Belger et al., 2024).

Currently, the popularity of natural drugs derived from plants has been increasing, as they are considered to have fewer side effects, are non-toxic, economical, and easily accessible. One commonly used example is bromelain, which is a combination of several thiol endopeptidases derived from the fruit, stem, and root of the pineapple Ananas comosus. Bromelain has been reported to be effective in preventing cardiovascular disease, particularly in reducing the incidence of transient cardiomyopathy through its ability to dissolve thrombi and decrease blood viscosity (Varilla et al., 2021). Cardiac troponins T and I are components of the cardiomyocyte contractile apparatus that serve as biomarkers for myocardial injury. Their measurement is minimally invasive, less expensive compared to imaging tests, and demonstrates a high negative predictive value (Dulf et al., 2023; Rawat et al., 2021; Sebayang, 2021).

This study will evaluate the cardioprotective effect of bromelain on troponin T and troponin I levels as markers of cardiotoxicity in Wistar rats induced with doxorubicin. It is therefore expected that bromelain may be utilized as a plant-based therapy to prevent myocardial injury and reduce cardiovascular disease (CVD)-related mortality in cancer patients receiving doxorubicin.

MATERIALS AND METHODS

Sample

This study is an experimental research with a posttest-only control group design conducted in vivo using male Wistar rats (Rattus norvegicus), aged 8 weeks and weighing between 150–200 g. The rats were housed in polypropylene cages at the Experimental Animal Laboratory, Faculty of Veterinary Medicine, Universitas Airlangga, equipped with feeding and drinking facilities under controlled conditions at a temperature of 22 ± 2 °C. Each cage contained five rats, with ad libitum access to food and water. Randomization was performed using a single-blind method. Following randomization, the rats underwent an acclimatization period prior to the initiation of the research intervention.

Materials

The drug used in the treatment was doxorubicin HCl, obtained from PT CKD OTTO Pharmaceuticals, Indonesia. Bromelain used in this study contained 2000 Gelatin Digestive Units (GDU/gram) at a dosage of 10 mg/kg, with a Certificate of Analysis (Bromelain CAS Number: 37189-34-7, EC Number: 253-387-5), supplied by PT Gama Biotek Indonesia Laboratory, Malang, East Java. The materials for the immunoassay evaluation of troponin I and troponin T consisted of reagents from the ELISA Kit: TNNI2 Troponin I, Fast Skeletal Muscle, and TNNT1 Troponin T, Slow Skeletal Muscle, developed by BT Lab Bioassay Technology Laboratory, Zhejiang, China.

Dose selection

The doxorubicin dosage administered during treatment was 15 mg/kg body weight, delivered via intraperitoneal injection. The bromelain dosage administered during treatment was 40 mg/kg body weight, delivered enterally at 6.2 ml/day using a gastric gavage, 30 minutes prior to doxorubicin HCl administration.

Design

A total of 15 adult male Wistar rats were included in the study and divided into three groups, each consisting of five rats (n = 5). The experimental animals were grouped and treated as follows:

1. Normal group (P1): Rats received no treatment and were given continuous access to food and water ad libitum for two weeks.
2. DOX group (P2): Rats were administered DOX (15 mg/kg, i.p.) every other day for two weeks.
3. DOX + Br 40 mg/kg group (P3): Rats were administered DOX (15 mg/kg, i.p.) and Br (40 mg/kg, p.o.) 30 minutes prior to each DOX administration.

The intervention was carried out for 14 days, and experimental units were obtained from the serum of Wistar rats in each group at the end of the intervention. On day 15, a total of 5 ml of blood samples were collected from each rat in all treatment groups to measure troponin T and troponin I levels as biomarker indicators of myocardial injury.

Measurement of cardiac injury biomarkers

The measurement of troponin T and troponin I levels in rat blood was performed by collecting 5 ml of intracardiac blood after 14 days of treatment in the three experimental groups. Blood samples were treated with anticoagulant and subsequently transferred to the Clinical Pathology Laboratory, Institute of Tropical Disease, Airlangga University, Surabaya. The blood was centrifuged for 20 minutes at 3000 rpm, and the supernatant was collected without sediment. Supernatant samples were stored at –20 °C while reagent preparation was conducted. Measurement of troponin T and troponin I was carried out using an immunoassay method through ELISA (Enzyme-Linked Immunosorbent Assay). The instrument used in this study was the iMark Microplate Absorbance Reader (Bio-Rad Laboratories, Inc.). Measurements were performed at a wavelength of 450 nm, with results expressed in ng/ml.

Statistical analysis

The primary data obtained were subjected to editing, coding, and entry into a computer using SPSS software version 16.0 for Windows (SPSS Inc., Chicago, IL). After data cleaning, descriptive analysis was performed by presenting the mean, standard deviation, and box-plot diagrams for each group. Comparative statistical analysis of unpaired numerical data among the three groups was conducted using one-way ANOVA, followed by Bonferroni post hoc testing. A p-value ≤ 0.05 was considered statistically significant.

RESULT

Characteristic of sample

This in vivo study, using a posttest-only control group design, used Wistar rats (Rattus norvegicus) selected based on their good general condition, stable physiological data, and normal activity. Five rats were required for each treatment. The criteria used included rats aged 8 weeks and weighing between 150 and 200 grams. The initial characteristics of each group are shown in Table 1.

Table 1. Characteristic of Wistar rats

Characteristics	P1 (n=5)	P2 (n=5)	P3 (n=5)
Species	*Rattus norvegicus* strain Wistar		
Age	8 weeks		
Sex	male		
Condition	Good condition, normal behavior		
Weight (mean)	152-194 (178,8) gram	150-196 (178,6) gram	153-200 (178,4) gram

Table 2. Mean of sample body weight

Group	N	Weight (mean) ± SD	*p*
Control (P1)	5	178,8 gram ± 16,27	
Doxorubicin 15 mg/kgBW (P2)	5	178,6 gram ± 18,21	0,09
Doxorubicin 15 mg/kgBW + Bromelain 40 mg/kgBW (P3)	5	178,4 gram ± 17,5	

It was found that the average body weight of each group was not much different, namely 178.8 grams ± 16.27 for group P1, 178.6 grams ± 18.21 for group P2, and 178.4 grams ± 17.5 for group P3. A normality test was conducted on the body weight characteristics of the experimental animals. The test results showed a significance value of p = 0.09 (p> 0.05), which indicates that the data has a normal distribution.

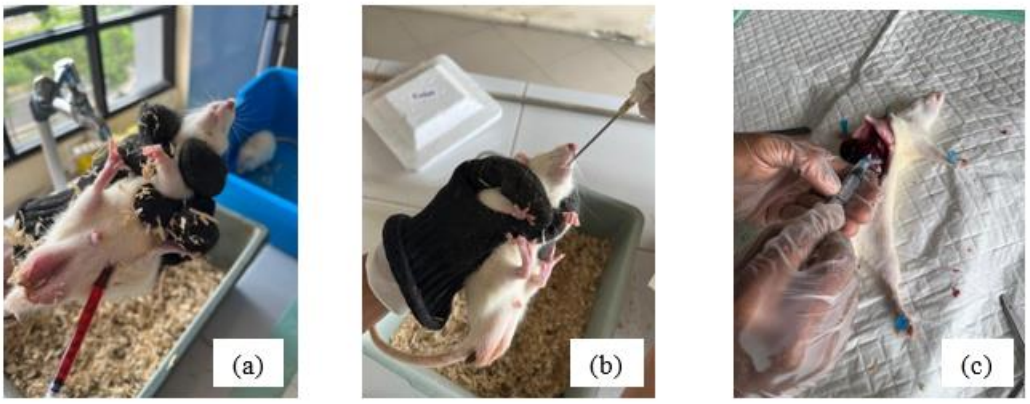

Figure 1. (a) Doxorubicin administration; (b) Bromelain administration; (c) Blood sample collection

Wistar rats (Rattus norvegicus) were used because they are representative of the human biological system and have a faster metabolic rate, which supports the efficiency of experimental studies. The rats with an initial weight between 150-200 grams. The Normality and homogeneity tests results showed a significance value of p>0.05. This significance value indicates that at the beginning of the study, all mice were in comparable condition and met the established criteria, thus minimizing factors that could cause bias. Another criteria in this study was to use mice that were 8 weeks old, at which age the mice had reached physiological maturity, including full development of vital systems and attainment of sexual maturity, so they were considered representative for the purposes of experimental studies.

Cardioprotective effect of bromelain on doxorubicin-induced myocardial injury

To assess doxorubicin-induced cardiotoxicity, myocardial injury biomarkers were measured as indicators of cardiac tissue damage. After 14 days, 5 mL of blood samples were collected from each rat in each treatment group to determine troponin T and troponin I levels as biomarkers of myocardial damage.

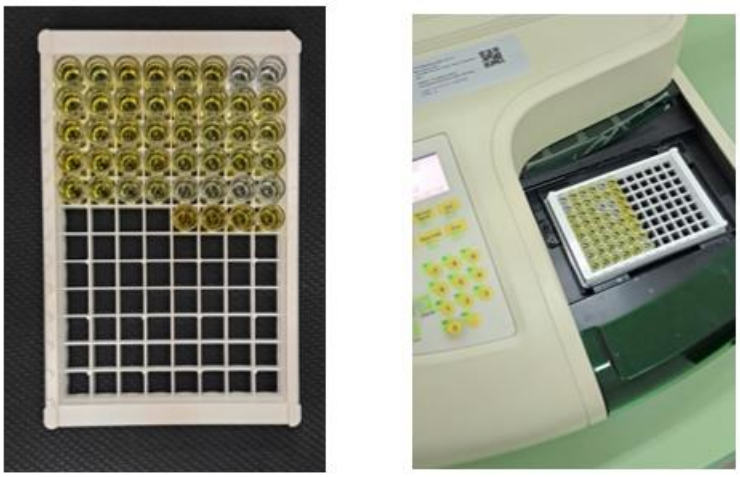

Figure 2. (a) Sample preparation; (b) Measurement of troponin T and troponin I using absorbance reader

Descriptive analysis was then performed on troponin T and troponin I levels in each test animal from each group, namely the control group (P1), group P2, and group P3. One-way ANOVA analysis showed that the mean troponin T level increased in the doxorubicin group (P2) compared with the normal group ($p < 0.001$). The mean troponin I level also increased in the P2 group compared with P1 ($p < 0.001$) (Figure 1). Post-hoc Bonferroni testing revealed a significant difference in troponin T levels between P1 and P2 ($p < 0.001$; 95% CI: –0.61 to –0.26 ng/ml), as well as in troponin I levels between P1 and P2 ($p < 0.001$; 95% CI: –0.508 to –0.152 ng/ml).

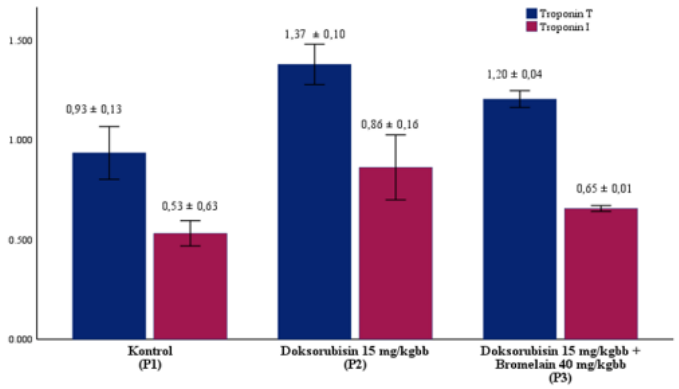

Figure 2. Histogram of mean and standard deviation of troponin T and troponin I

Administration of bromelain at a dose of 40 mg/kg significantly reduced cTnT and cTnI levels compared with the group that received doxorubicin alone. In the P3 group, the mean troponin T level showed a significant decrease compared with the P2 group ($p < 0.001$). Similarly, the mean troponin I level demonstrated a significant reduction compared with the P2 group ($p < 0.001$) (Table 2).

Table 2. Results of One-Way ANOVA for Troponin T and Troponin I Levels

Group	N	Troponin T (mean ± SD)	Troponin I (mean ± SD)	*p-value*
Control (P1)	5	0,93 ± 0,13 ng/ml	0,53 ± 0,63 ng/ml	
Doxorubicin 15 mg/kg (P2)	5	1,37 ± 0,10 ng/ml	0,86 ± 0,16 ng/ml	<0,001
Doxorubicin 15 mg/kg + Bromelain 40 mg/kg (P3)	5	1,20 ± 0,04 ng/ml	0,65 ± 0,01 ng/ml	

Post-hoc Bonferroni testing revealed a significant difference in troponin T levels between P2 and P3 ($p = 0.05$); The 95% CI for

troponin T levels between P2 and P3 was 0.17 to –0.0005 ng/mL, while for troponin I levels between P2 and P3 it was 0.20 to 0.028 ng/mL (p = 0.022). These findings indicate that bromelain was effective in reducing doxorubicin-induced cardiac injury in Wistar rats.

Table 3. Post-Hoc Bonferroni test for cardiac troponin T

Group	Mean	95% CI		*p-value*
	Difference	Maximum	Minimum	
Group P1 vs Group P2	-0,33 ng/ml	-0,508 ng/ml	-0,152 ng/ml	<0,001
Group P1 vs Group P3	-0,40 ng/ml	-0,76 ng/ml	-0,49 ng/ml	0.025
Group P2 vs Group P3	0,20 ng/ml	0,028 ng/ml	0,384 ng/ml	0,022

Table 4. Bonferroni Post-Hoc Test results for cardiac troponin I

Group	Mean	95% CI		*p-value*
	Difference	Maimum	Minimum	
Group P1 vs Group P2	-0,44 ng/ml	-0,61 ng/ml	-0,26 ng/ml	<0,001
Group P1 vs Group P3	-0,36 ng/ml	-0,42 ng/ml	-0,36 ng/ml	0.024
Group P2 vs Group P3	0,17 ng/ml	-0,0005 ng/ml	- 0,348 ng/ml	0,05

DISCUSSION

Effect of doxorubicin on cardiac troponin levels

The mean troponin T and troponin I levels in the normal group (P1), which did not receive any treatment, remained low (0.93 ± 0.13; 0.53 ± 0.63 ng/mL). Low plasma troponin levels reflect a healthy cardiovascular system (Romann et al., 2024); therefore, the results in group P1 indicate the absence of myocardial injury in the rats. The mean troponin T level (1.37 ± 0.10 ng/mL; $p < 0.001$) and troponin I level (0.86 ± 0.16 ng/mL; $p < 0.001$) in the doxorubicin group were significantly elevated compared with the normal group, indicating that doxorubicin increased troponin T and troponin I levels. These findings demonstrate that doxorubicin induction exerts cardiotoxic effects on Wistar rat cardiomyocytes. Most previous experimental studies on the cardiotoxic effects of doxorubicin in animal models have reported results consistent with the present findings.

An increase in serum troponin levels showed in rats on day 4 after doxorubicin induction at a dose of 15 mg/kg body weight. The experimental criteria in that study were similar to the present research, namely Wistar rats aged 8 weeks with an initial body weight between 150–200 g (Sandamali et al., 2019). Troponin T levels increased at 4 hours and continued to rise until 8 hours after doxorubicin administration, while serum troponin I peaked at 8 hours. However, both biomarkers did not show significant increases compared with the control group after 24 hours (Pan et al., 2022).

Cardiotoxic side effects of doxorubicin have also been observed in non-experimental studies involving human subjects. A prospective cohort study by Demissei et al. measured troponin T levels repeatedly in 323 breast cancer patients undergoing anthracycline therapy, including doxorubicin, with a follow-up of 3.7 years. The results showed an early increase in troponin T (hs-cTnT). An hs-cTnT level >14 ng/L at the end of anthracycline therapy was associated with a two-fold increased risk of cancer therapy-related cardiac dysfunction such as that caused by doxorubicin (HR: 2.01; 95% CI: 1.00–4.06) (Demissei et al., 2020). A meta-analysis of 61 studies involving 5,691 patients treated with anthracyclines, including doxorubicin, showed that cancer therapy was associated with elevated troponin levels (OR 14.3; 95% CI: 6.0–34.1; n = 3049). This association was most prominent in high-dose chemotherapy regimens (Michel et al., 2020).

Troponin is a highly specific cardiac biomarker that reflects myocardial cell death or apoptosis and has been well established as a diagnostic standard for acute myocardial infarction, as well as for detecting both acute and chronic myocardial injury (Romann et al., 2024). Doxorubicin, a potent chemotherapeutic agent with well-documented cardiotoxic potential, is known to trigger elevated troponin levels through its capacity to induce structural and functional damage to cardiomyocytes (Tzolos et al., 2020). Doxorubicin promotes the generation of reactive oxygen species (ROS), inducing excessive oxidative stress. The mechanism underlying ROS overproduction occurs intracellularly, where doxorubicin binds to cardiolipin, a component of the inner mitochondrial membrane. Doxorubicin disrupts the cellular redox cycle and impairs mitochondrial function (Ajaykumar et al., 2020). Necrotic cardiomyocytes release troponins, which therefore have high sensitivity and specificity for myocardial infarction diagnosis. In irreversible myocardial injury, troponin release is caused by apoptosis or necrosis of cardiomyocytes, whereas in reversible injury, troponin release results from increased membrane permeability or the formation and release of membrane vesicles (Sorodoc et al., 2022).

Changes in troponin levels may be influenced by both the administered dose and the duration of exposure. An experimental study by Sandamali et al. tested the cardiotoxicity of doxorubicin in animal models. Rats were randomly divided into eight groups, each receiving escalating doses of doxorubicin (13, 14, 15, 16, 17, 18, 19, and 20 mg/kg). The study showed a progressive and significant increase in cTnI concentrations in rats treated with doxorubicin, beginning at the lowest dose of 13 mg/kg and peaking at 20 mg/kg, with the highest levels observed at the maximum dose (Sandamali et al., 2019). In another experiment by Pan et al., rats received doxorubicin at 1, 2, or 3 mg/kg weekly via tail vein injection for 2, 4, 6, or 7 weeks. Biomarker changes were observed at weeks 2, 4, 6, and 8. cTnI levels in the low-dose group increased significantly at week 8, whereas in the medium- and high-dose groups, cTnI levels increased significantly starting from week 2 (Pan et al., 2022).

Follow-up analysis using the post-hoc Bonferroni test revealed significant differences consistent with the one-way ANOVA results. A significant reduction was observed in both troponin T and I levels between the P2 and P3 groups ($p = 0.05$; 95% CI: –0.0005 to 0.348 ng/mL), ($p < 0.022$; 95% CI: 0.028–0.384 ng/mL). These findings support the hypothesis of this study that bromelain exerts a cardioprotective effect on the myocardial cells of Wistar rats induced with doxorubicin by preventing elevations in cTnT and cTnI. The increase in troponin levels following doxorubicin administration is closely associated with oxidative stress. Doxorubicin promotes excessive ROS generation, leading to oxidative stress that triggers necrosis or apoptosis of cardiomyocytes, thereby resulting in troponin release as an indicator of myocardial injury (Sabina et al., 2021; Ajaykumar et al., 2020).

An antioxidant therapeutic approach is widely applied in managing doxorubicin-induced cardiotoxicity. Bromelain has been shown to exert strong cardioprotective effects through its ability to scavenge free radicals, thereby reducing oxidative stress (Kansakar et al., 2024). An experimental study by Chen et al. demonstrated that bromelain treatment protects against oxidative stress via activation of transcription factor EB (TFEB). Bromelain induces TFEB activation, which enhances the expression of autophagy- and antioxidant-related proteins while reducing oxidative stress in rats. Bromelain-induced overexpression of TFEB plays a role in suppressing intracellular ROS accumulation (Chen et al., 2023).

Bromelain can enhance Akt phosphorylation, thereby inhibiting cell apoptosis. Bromelain administration resulted in statistically significant improvement in left ventricular function during the reperfusion phase. The cardioprotective effect of bromelain is thought to derive from the inhibition of programmed cell death through activation of the Akt–FOXO signaling pathway. Bromelain enhances phosphorylation of Akt kinase (active form) and promotes its translocation into the nucleus, where it phosphorylates FOXO3a and suppresses apoptotic signaling. The protective effects of bromelain on myocardial ischemia include preventing blood flow stasis, reducing interstitial edema, and improving microcirculation (Hikisz et al., 2021).

CONCLUSION

Bromelain demonstrated cardioprotective efficacy by significantly suppressing the elevation of cTnT and cTnI concentrations in the myocardial tissue of Wistar rats induced with doxorubicin.

Ethics approval

This study was approved by the Animal Care and Use Committee (ACUC) of Veterinary Medicine Faculty, Airlangga University, Surabaya, Indonesia. All animal procedures complied with established ethical guidelines for the care and use of laboratory animals.

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