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Hematological and Biochemical Alterations of Andaliman (*Zanthoxylum Acanthopodium* Dc) with Doxorubicin Induced in White Wistar Rat

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ABSTRACT
Doxorubicin, a well-known chemotherapy drug, is associated with cardiac toxicity primarily due to oxidative stress. This oxidative stress leads to the production of reactive oxygen species and a subsequent decline in antioxidant levels. As doxorubicin induces the formation of free radicals and decreases endogenous antioxidants, it triggers various hematological and biochemical abnormalities. Consequently, the use of antioxidants has been proposed as a strategy to mitigate this damage. This study focuses on the administration of ethanol extract from Andaliman (EAF) fruit, recognized for its rich array of metabolites and antioxidant properties, which may serve as a cardioprotective agent against the adverse effects of doxorubicin. The research involved comprehensive observations, including hematological and clinical chemistry examinations. The findings indicate that EAF demonstrates protective effects by enhancing hematological and clinical chemistry parameters in male Wistar rats subjected to doxorubicin. Notably, these improvements were statistically significant when compared to the control group. Given its promising results, further exploration of EAF as a protective agent for hematological and biochemical health warrants attention and development.
Keyword: Andaliman, Doxorubicin, Hematological, Biochemical, Cardioprotective

ABSTRAK
Doksorubisin merupakan obat kemoterapi yang terkenal, dikaitkan dengan toksisitas jantung terutama karena stres oksidatif. Stres oksidatif menyebabkan produksi spesies oksigen reaktif dan penurunan kadar antioksidan. Karena doksorubisin menginduksi pembentukan radikal bebas dan menurunkan antioksidan endogen, doksorubisin memicu berbagai kelainan hematologi dan biokimia. Sehingga, penggunaan antioksidan telah diusulkan sebagai strategi untuk mengurangi kerusakan yang disebabkan doksorubisin. Penelitian ini berfokus pada pemberian ekstrak etanol dari buah Andaliman (EEA), yang dikenal karena rangkaian metabolit dan sifat antioksidannya yang tinggi, yang dapat berfungsi sebagai agen kardioprotektif terhadap efek samping doksorubisin. Penelitian ini melibatkan pengamatan komprehensif, termasuk pemeriksaan hematologi dan biokimia klinis. Temuan menunjukkan bahwa EEA menunjukkan efek perlindungan dengan meningkatkan parameter hematologi dan biokimia klinis pada tikus wistar jantan yang diberi doksorubisin. Hasilnya, secara statistik menunjukkahn peningkatan yang signifikan jika dibandingkan dengan kelompok kontrol. Mengingat hasil yang menjanjikan, eksplorasi lebih

lanjut terhadap EEA sebagai agen pelindung untuk kesehatan hematologi dan biokimia perlu mendapat perhatian dan pengembangan.
Kata Kunci: *Andaliman, Doksorubisin, Hematologi, Biokimia, Kardioprotektif*

1. Introduction

Doxorubicin is a potent medication widely used in the treatment of various cancers. However, its clinical application is somewhat restricted due to its specific toxic effects on cardiac tissues [1]. Notably, there have been documented instances of congestive heart failure, cardiomyopathy, and changes in electrocardiographic patterns following the administration of combined doses of Doxorubicin [2]. The cardiotoxic effects of this drug are attributed to several mechanisms, including free radical-induced myocardial injury, lipid peroxidation [3], mitochondrial damage [4], a decrease in Na^+–K^+ adenosine triphosphate activity [5] , the release of vasoactive amines [6] , and overall cellular toxicity [7] . Additionally, oxidative stress and the generation of free radicals [8], such as superoxide anions and other reactive oxygen species [9], play significant roles in these adverse effects. Although Doxorubicin is among the most effective anti-cancer agents available, its use is constrained by the risk of cumulative, dose-dependent cardiac toxicity, which can lead to irreversible heart failure in many patients [10]. This drug operates by intercalating into nuclear DNA, disrupting protein synthesis, generating reactive oxygen species, and inhibiting topoisomerase II, an enzyme crucial for DNA transcription and replication [11]. Cardiotoxicity rates associated with Doxorubicin range from 3% to 26% in treated patients, compared to 2% to 28% with trastuzumab and 2. 7% to 11% with sunitinib. A recent retrospective study found that 6. 6% of breast or hematologic cancer patients who underwent chemotherapy developed heart failure [12]. In light of these concerns, some research has focused on exploring phytochemicals that may provide a neutralizing effect against the cardiotoxicity of Doxorubicin [13].

One notable endemic plant species in Indonesia recognized for its cardioprotective properties is Andaliman (Zanthoxylum acanthopodium DC.) [14,15]. The fruit of Andaliman contains a variety of compounds, including flavonoids, pyrroloquinoline alkaloids, terpene alkaloids, porphyrin alkaloids, benzophentridine alkaloids, quaternary isoquinoline alkaloids, and terpenoids such as geranyl acetate. Its aroma is predominantly citrus, featuring scents like citronellol and limonene. Additionally, it contains other compounds such as E-1-decanal, linalool, β-myrcene, β-ocimene, glycosides, saponins, tannins, steroids, and more [15,16]. Pharmacological studies indicate that extract from Andaliman exhibits both anti-free radical and cardioprotective effects [10,17,18]. The flavonoids present in the fruit are particularly noteworthy for their antioxidant properties, which help mitigate oxidative stress by inhibiting the formation of free radicals induced by doxorubicin [16,19]. We also assessed hematology and clinical chemistry levels to evaluate the protective effects of the extract on the blood profile. Quercetin served as a comparison due to its known cardioprotective and antioxidant properties, which contribute to the prevention of cardiovascular disease [20–22].

2. Materials and Methods

2.1 Plants, Tools, and Materials

Andaliman fruit was taken from Onan Runggu, Samosir Regency, North Sumatra and identified at the Biology Research Center of the Indonesian Institute of Sciences with the number 332/IPH.1.01/lf.07/II/2016. The tools used in this research were analytical balance (Mettler Toledo, Greifensee, Switzerland), light microscope (Zeiss, Ober-kochen, Germany), a 1 mL syringe (OneMed, Surabaya, Indonesia), a 3 mL syringe (OneMed, Indonesia), microtube, surgical instruments, laboratory glassware, oral sondes, animal scales, refrigerator, vortex, hematology analyzer (Sysmex), chemistry analyzer (Cobas C501), and spectrophotometer. Meanwhile, the materials used in this research were doxorubicin HCl (KalbeMed), ketamine (Bernofarm),

quercetin (Sigma), Sodium CMC 0.5% suspension (Sigma), EDTA (Ethylenediamine Tetra-Acetic Acid) (Sigma), Aquades (Smart Lab), and Ethanol (Smart Lab).

2.2 Preparation of Extract

The freshly harvested Andaliman fruit was meticulously cleaned to eliminate any dirt or contaminants, then drained and weighed to determine its moist weight. Following this, the fruit was completely dried in a drying cabinet. Once dried, it was blended into a fine powder and stored in a plastic bag at room temperature. For the extraction process, the Andaliman simplicia powder was macerated by soaking it in 70% ethanol. Specifically, a vessel was filled with 7.5 liters of 70% ethanol and one kilogram of finely ground simplicia powder. The vessel was then covered and set aside for five days, protected from light while being stirred periodically. After the five-day period, the mixture was filtered, and the remaining dregs were pressed to extract additional liquid. These dregs were washed with 70% ethanol, stirred, and combined until a total of 10 liters of macerate was achieved. The next step involved draining the macerate into a sealed container, which was kept away from direct sunlight for two days. To concentrate the extract, a rotary evaporator was employed, followed by drying it with a freeze-dryer [23,24].

2.3 Animal Design and Research

Male Wistar rats, weighing between 180 and 200 grams, were housed in a controlled environment with continuous access to food and water. The procedures involving animal use have been approved in accordance with the guidelines set forth by the Animal Research Ethics Committee of the Faculty of Mathematics and Natural Sciences at Universitas Sumatera Utara, as indicated by letter number 0225/KEPH-FMIPA/2024. The study comprised seven groups of animals, each consisting of five subjects. All treatments, except for the standard control group, were administered once daily over a span of seven consecutive days. On the eighth and ninth days, doxorubicin was administered via intraperitoneal injection at a dosage of 10 mg/kg body weight, one hour following the administration of the assigned preparation. The division of the groups and the experimental timeline are illustrated in Figure 1.

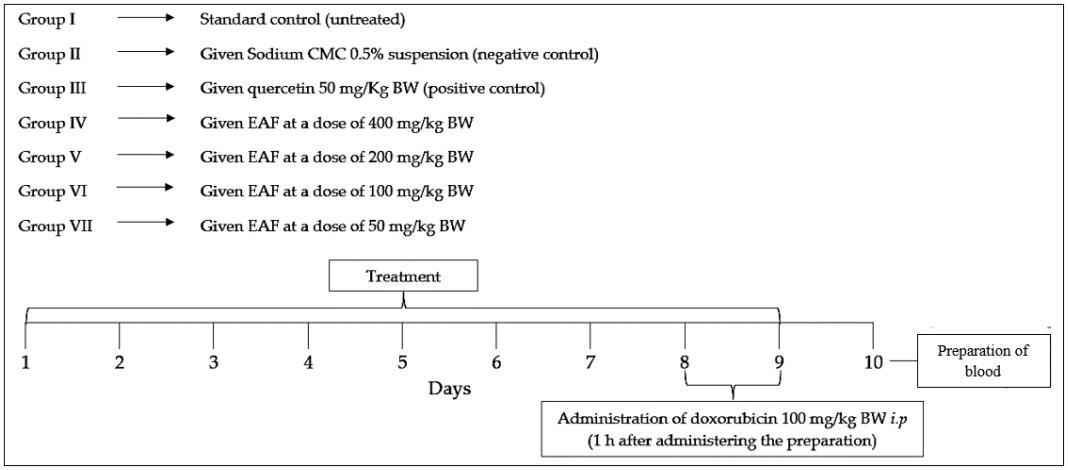

Figure 1. The division of the groups and the experimental timeline

2.4 Preparation of Blood Serum

Blood were collected on the tenth day or after the rats had fasted for twelve hours. After being given ketamine anaesthesia, the rats were dissected, and a 1 mL syringe was used to draw blood directly from the rat's heart up to ±5 mL; the blood was put into a microtube and left for ±30 minutes. The blood was centrifuged at 3000 rpm for 20 minutes to obtain rat blood serum [16,25].

2.5 Hematology Examination Procedure

Blood is taken from the heart (intracardiac) slowly using a sterile syringe as much as 1-3 ml, then inserted into a projection tube containing EDTA anticoagulant and immediately homogenized slowly without lysing the blood cells. Hematology examinations at the Integrated Laboratory of the Universitas Sumatera Utara Hospital include the amount of hemoglobin, hematocrit, leukocytes, erythrocytes, platelets, neutrophils segments, lymphocytes, monocytes, eosinophils, and basophils [16,25].

2.6 Clinical Chemistry Examination Procedure

The blood taken is inserted into a microcentrifuge tube as much as 1 mL and left at room temperature for 10 minutes. Then, it was centrifuged for 10 minutes at a speed of 3000 rpm until a clear serum was produced. Clinical chemistry levels of blood serum were analyzed using a spectrophotometer; examinations included BUN (Blood Urea Nitrogen), total bilirubin, AST (Aspartate Aminotransferase), ALT (Alanine Aminotransferase), and creatinine levels. The level was determined by reacting 100 µl of test serum with 1000 µl of reagent in 30 test tubes of 5 ml each, homogenized with the help of a vortex. Absorbance was measured with the help of a spectrophotometer at a temperature of 37^{o}C exactly after the 1st, 2nd, and 3rd minutes at a wavelength of 340 nm. The same was done for the blank (reagent + aquadest). BUN, total bilirubin, AST, ALT, and creatinine levels were determined by calculating the mean difference in sample absorbance per minute multiplied by a factor of 1745 [25]. Clinical biochemical measurements were carried out at the Integrated Laboratory of the Universitas Sumatera Utara Hospital.

3. Result and discussion

3.1 Hematology Observation Results\

Hematology observation aims to assess the blood profile in rats after doxorubicin induction. Observations are made by measuring the levels of hemoglobin, hematocrit, leukocytes, erythrocytes, platelets, segmented neutrophils, lymphocytes, monocytes, eosinophils, and basophils. The results of the observations can be seen in Table 1.

Table 1. Results of Hematology Observation

Group	Untreated (Normal)	S-CMC 0.5%	Quercetin 50 mg	EAF 400 mg	EAF 200 mg	EAF 100 mg	EAF 50 mg
Hemoglobin (g/dL)	14.14 ± 0.56 [b]	9.92 ± 2.22 [a]	13.10 ± 0.78	12.60 ± 1.76	12.40 ± 1.07	11.40 ± 2.75	11.30 ± 2.03
Hematocrit (%)	42.98 ± 5.34	32.24 ± 4.87	42.68 ± 3.40	42.34 ± 1.99	38.64 ± 2.48	37.52 ± 6.39	37.00 ± 12.40
Leukocytes (10^3/µL)	7.01 ± 1.17	4.136 ± 1.32	5.07 ± 1.74	4.76 ± 1.80	4.67 ± 2.04	4.46 ± 0.63	4.37 ± 1.92
Erythrocytes (10^3/µL)	7.56 ± 0.24	5.51 ± 1.56	7.21 ± 0.77	7.06 ± 0.71	6.64 ± 1.34	6.47 ± 1.58	6.11 ± 1.51
Platelets (10^3/µL)	749.00 ± 320.35 [b]	412.80 ± 157.39 [a]	637.80 ± 71.71	635.80 ± 76.28	572.00 ± 187.38	545.00 ± 37.89	466.80 ± 111.17
Neutrophils segments (%)	53.36 ± 15.83 [ac]	4.34 ± 2.90 [a]	49.62 ± 7.34 [a]	42.98 ± 6.74 [a]	42.70 ± 18.00 [a]	41.58 ± 15.26 [a]	36.48 ± 15.82 [a]
Lymphocytes (%)	62.44 ± 8.77 [ab]	23.04 ± 14.04 [ac]	48.56 ± 17.66 [ab]	46.10 ± 12.78 [b]	46.10 ± 12.78 [b]	41.38 ± 12.86 [b]	33.40 ± 8.57 [a]
Monocytes (%)	8.36 ± 4.44	23.20 ± 16.42	8.94 ± 3.06	12.26 ± 8.10	19.36 ± 3.32	21.56 ± 17.28	22.48 ± 24.98
Eosinophils (%)	4.54 ± 3.93	0.26 ± 0.31 [a]	0.28 ± 0.31 [b]	0.69 ± 0.62 [a]	0.64 ± 0.64 [a]	2.04 ± 1.9	2.86 ± 1.31
Basophils (%)	3.68 ± 1.78 [bc]	0.42 ± 0.34 [a]	0.68 ± 0.36 [a]	0.66 ± 0.27 [a]	0.64 ± 0.15 [a]	0.48 ± 0.44 a	0.44 ± 0.45 [a]

[a]: significantly different from the untreated group ($p < 0.05$); [b]: significantly different from the 0.5% S-CMC 0.5% group ($p < 0.05$); [c]: significantly different from the quercetin group ($p < 0.05$).

The observation results showed that the S-CMC 0.5% group experienced a significant decrease in hemoglobin, hematocrit, leukocytes, erythrocytes, platelets, segmented neutrophils, lymphocytes, eosinophils, and basophils, while the monocyte value increased. Many reports have discussed the effect of doxorubicin on changes in hematological levels [55]. The observation showed that the quercetin group had levels closest to the untreated group. The group that received EAF had levels significantly different from the S-CMC 0.5% group, indicating that EAF improved the hematological parameters of rat blood after doxorubicin induction.

3.2 Clinical Blood Biochemistry Observation

The blood biochemistry observations included BUN (urea nitrogen), total bilirubin, AST, ALT, and creatinine. The results of blood biochemistry measurements can be seen in Table 2.

Table 2. Results of Clinical Blood Biochemistry Observations

Group	BUN (mg/dL)	Total bilirubin (mg/dL)	AST (U/L)	ALT (U/L)	Creatinine (mg/dL)
Untreated (Normal)	18.59 ± 0.06 [bc]	0.33 ± 0.01 [bc]	150.20 ± 11.50 [bc]	42.20 ± 4.50 [bc]	0.37 ± 0.12 [b]
S-CMC 0.5%	25.69 ± 0.06 [ac]	0.94 ± 0.03 [ac]	459.20 ± 12.13 [ac]	94.60 ± 3.84 [ac]	1.25 ± 0.23 [ac]
Quercetin 50 mg	19.89 ± 0.06 [ab]	0.38 ± 0.01 [ab]	180.20 ± 15.66 [ab]	53.20 ± 4.09 [ab]	0.37 ± 0.24 [b]
EAF 400 mg	20.89 ± 0.06 [abc]	0.39 ± 0.03 [ab]	247.80 ± 17.24 [abc]	62.80 ± 3.27 [abc]	0.38 ± 0.23 [b]
EAF 200 mg	22.69 ± 0.06 [abc]	0.50 ± 0.01 [abc]	273.40 ± 16.37 [abc]	64.60 ± 3.51 [abc]	0.45 ± 0.16 [abc]
EAF 100 mg	23.65 ± 0.11 [abc]	0.74 ± 0.02 [abc]	278.80 ± 17.24 [abc]	73.40 ± 2.88 [abc]	0.75 ± 0.13 [abc]
EAF 50 mg	24.79 ± 0.06 [abc]	0.89 ± 0.01 [abc]	322.40 ± 11.64 [abc]	75.60 ± 3.97 [abc]	0.83 ± 0.32 [abc]

[a]: significantly different from the untreated group ($p < 0.05$); [b]: significantly different from the 0.5% S-CMC 0.5% group ($p < 0.05$); [c]: significantly different from the quercetin group ($p < 0.05$).

Doxorubicin induction causes an increase in BUN, total bilirubin, AST, ALT, and creatinine levels. Observations in Table 4 show that the S-CMC 0.5% group has a significantly different average from the untreated group ($p < 0.05$). The quercetin group also has a significant difference with the S-CMC 0.5% group ($p < 0.05$), indicating that administration of 50 mg/kg BW quercetin can reduce BUN, total bilirubin, AST, ALT, and creatinine levels in rats after doxorubicin induction. The results of statistical analysis of EAF administration also showed a significant difference with the S-CMC 0.5% group, which also indicated that EAF administration could affect BUN, total bilirubin, AST, ALT, and creatinine levels in rats after doxorubicin induction.

The adverse reactions associated with chemotherapeutic agents pose significant challenges, as they constrain both the dosage and duration of treatment while also impacting patients' quality of life. This issue has captured the attention of researchers for over fifty years. In this study, we observed the toxicity induced by doxorubicin (DOX), which was found to cause liver and kidney damage. This was evidenced by increased levels of serum markers such as ALT (alanine aminotransferase), AST (aspartate aminotransferase), total serum bilirubin (TSB), and blood urea nitrogen (BUN), indicating DOX's capacity to induce hepatorenal toxicity [16]. Unfortunately, the therapeutic use of DOX is significantly hampered by its dose-dependent toxic effects, particularly concerning severe cardiac and liver toxicity [26]. Doxorubicin poisoning can be categorized into acute, subacute, and chronic toxicity. Acute toxicity typically arises after a single administration or a brief treatment period, with common symptoms including hypotension, arrhythmia, and cardiac dysfunction. These symptoms may be sporadic and are often coupled with liver and kidney damage [16,17]. The current study highlights that the use of a single high-dose model of Doxorubicin (DOX) toxicity is prevalent, providing valuable insights into the organ injuries induced by this drug. Our findings indicate a significant increase in the levels of AST, ALT, total serum bilirubin (TSB), and blood urea nitrogen (BUN) in the rat model [27,28]. ALT and AST are crucial enzymes involved in the metabolism of sugars and proteins. While ALT is primarily found in liver cells, AST is mainly present in myocardial cells; however, elevated serum levels of AST may also occur with liver damage. Consequently, the rise in serum ALT and AST levels is indicative of liver injury. The increased activity of these aminotransferases might result from the leakage of enzymes from damaged liver cell membranes following DOX treatment[1]. Thus, these biochemical changes strongly suggest that DOX causes acute damage to both the liver and kidneys. Given the significant antitumor properties of DOX, there is a pressing need for novel strategies to mitigate its harmful side effects, potentially enhancing its effectiveness in cancer therapy [29].

4. Conclusion

In conclusion, we can observe the impact of doxorubicin-induced toxicity in a male wistar rat model, as evidenced by various biochemical and hematological abnormalities. Administration of andaliman fruit showed improvements in the condition of both hematology and clinical chemistry in test animals.

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