






Protective Activity of Beetroot Extract on Doxorubicin-Induced Hepatic and Renal Toxicity in Rat Model

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Abstract

BACKGROUND: The administration of doxorubicin can increase the production of reactive oxygen species (ROS) and disrupt the balance of antioxidant defenses triggered a cell damage including liver cells and renal cells. Antioxidant from medicinal plants have play role in protecting the cells against ROS. Beetroot tuber contains various phytochemical compound that has an antioxidant property.

AIM: The purpose of the study was to determine the protective effect of beetroot ethanol extract on concurrent use of doxorubicin for 15 days by measuring blood levels of aspartate aminotransferase, alanine aminotransferase, Creatinine, blood urea nitrogen and histopathological changes.

MATERIALS AND METHODS: Twenty-five male white rats as weighing 180–200 g were divided into five treatment groups. Group I was the normal control group, Group II was a negative control group that only injected doxorubicin with a cumulative dose of 15 mg/kg body weight (BW) for 15 days. Group III-V was the test group given beetroot extract (BE) at doses of 100, 200 and 400 mg, respectively, for 15 days with doxorubicin.

RESULTS: The group treated with BE at a dose of 200 mg/kg BW could improve serum levels of liver enzymes compared with negative controls ($p < 0.05$). The group treated with BE at a dose of 100 mg/kg BW also showed an improved effect on creatinine and BUN levels of rats compared to negative controls ($p < 0.05$). All parameters showed that the protective activity of beetroot ethanol extract was dependent on increasing the dose.

CONCLUSION: This research proves that the compound contained in beetroot ethanol extract has protective activity in liver and kidney of rats induced by doxorubicin.

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Introduction

The anticancer that is widely used as common therapy in cancer is doxorubicin. It is an anthracycline group that is isolated from *Streptomyces peucetius var caesius* [1]. The conditions of oxidative stress are closely related to doxorubicin therapy which is characterized by the formation of lipid peroxidation which has the potential to cause cell damage [2]. Doxorubicin toxicity can cause degeneration of organs such as the heart, kidneys, liver, and brain [3]. The chemical structure of doxorubicin has the potential to form free radicals through various mechanisms. Quinone groups in the tetracyclic ring of doxorubicin can release several superoxide radicals [4]. Doxorubicin metabolism also causes the formation of reactive aglycone metabolites and alcohol metabolites which can disturb the balance of iron intracellular concentrations [5]. The administration of doxorubicin can increase the production of reactive oxygen species (ROS) and disrupt the balance of antioxidant defenses so that it triggers a cell damage [6]. ROS are normally produced by the body in the process of metabolism, to overcome them, the body has a defense system against ROS by

producing antioxidant enzymes such as the enzyme of superoxide dismutase, catalase, glutathione and others so as not to trigger oxidative damage [7]. Excessive free radical production and reduced antioxidant defense system will cause cell damage. There have been many studies that proved the toxicity of doxorubicin to organs especially the heart, kidneys, and liver. The liver, as an organ that plays a role in metabolism, is one of the organs that have the potential to be damaged by the administration of doxorubicin. In addition, the kidneys will experience the same event due to high stress oxidative conditions. Several studies have shown that doxorubicin-induced liver and kidney damage by inflammatory processes, free radicals, oxidative stress, and lipid peroxidation [8], [9], [10]. To prevent the toxicity of doxorubicin to several body organs, it is necessary to have antioxidant supplementation to ward off free radicals from doxorubicin. One of the plants that have high antioxidant is beet tuber (*Beta vulgaris* L). Beetroot contains phytochemical constituents in the form of tannins, saponins, alkaloids, flavonoids, terpenoids, and steroids as well as content of betacyanins which have antioxidant effects [11]. Due to its phytochemical constituent, beetroot has a potential effect as protective agent in inhibiting the radical process of ROS. Based

on the description mentioned, this study was aimed to investigate the preventive effects of beetroot ethanol extract (*B. vulgaris* L.) in doxorubicin-induced liver and renal toxicity in rat.

Materials and Methods

Tools and materials

Rotary evaporator, whatmann filter paper no. 42, analytical balance (Boeco), light microscope (Boeco), distilled water, chloroform, beetroot, male white rats, ethanol 96% (Merck), CMC-Na (Bratachem), and doxorubicin (Kalbe).

Plant collection and extraction of beetroot

Beetroot tuber was collected from local market at Padang Bulan, North Sumatera, Indonesia. An amount of 300 g dried beetroot were crushed then macerated in ethanol 96% for 5 days. The products were evaporated with a rotary evaporator at a temperature of $\pm 50^{\circ}\text{C}$, then dried on a water bath [12].

Identification of phytochemical contents

Phytochemical screening carried out on ethanol extract beetroot included examining the secondary chemical metabolites of alkaloids, flavonoids, glycosides, tannins, saponins, terpenoids, and steroids [13], [14].

Animals and blood samples

Animals used in this study were 25 male Wistar rats, weighing 180–220 g. The blood samples were collected from inferior vein cava.

Experimental design

Rats were divided into 25 groups and each group consisted of 5 namely:

- Normal control: Normal tested groups without treatment
- Negative control: Group induced by accumulative dose of doxorubicin 15 mg/kg body weight (BW) + Na-CMC suspension
- Dose 100: Treated group that induced by accumulative dose of doxorubicin 15 mg/kg BW + extract dose of 100mg/kgBW
- Dose 200: Treated group that induced by accumulative dose of doxorubicin 15 mg/kg BW + extract dose of 200 mg/kg BW
- Dose 400: Treated group that induced by accumulative dose of doxorubicin 15 mg/kg BW + extract dose of 400 mg/kg BW.

Rats were induced using doxorubicin injection for 15 days with an accumulative dose of 15 mg/kg BW intraperitoneally, and the extract was given together during the 15 days doxorubicin range. On day 16th, the animals were anesthetized with chloroform, blood samples were collected then estimated the level of alanine aminotransferase (ALT), aspartate aminotransferase (AST), Creatinine and blood urea nitrogen (BUN).

Histological analysis

Microscopic examination on tissue section was conducted by slicing with a microtome after the liver and kidney have been embedded in paraffin with hematoxylin and eosin [15]. Observation was performed using a light microscope.

Statistical analysis

Statistical analysis was performed using analysis of variance with Tukey's Multiple Comparison Test. p-value for significance was set at 0.05. Values for all measurements were expressed as the mean \pm SD.

Results and Discussion

Phytochemical screening result of ethanol extract beetroot

The ethanol extract of beetroot contained of flavonoids, alkaloids, saponins, tannins, glycosides and steroids/terpenoid.

Effect of beetroot ethanol extract on ALT

In this research, ALT levels were examined from rats blood. The results of the levels obtained are presented in Table 1.

Table 1: Effect of Beetroot Extract (BE) Treatment on ALT level (U/L)

Group	ALT level (U/L)					Mean ALT \pm SD (U/L)
Normal Control	172.9	167.6	164.5	188.1	179.8	174.58 \pm 9.52*
Negative Control	453.8	423.3	429.8	488.3	412.9	441.62 \pm 30.11
BE 100 mg/kg BW	399.7	385	390.3	389.8	354.2	383.8 \pm 17.38
BE 200 mg/kg BW	337.3	296.2	331.2	286.7	290.1	308.3 \pm 24.02*
BE 400 mg/kg BW	247.2	234.1	241.7	257.9	248.6	245.9 \pm 8.80*

Data expressed as mean \pm SD (n = 5), *significant difference versus negative control group at P < 0.01. BW: Body weight, ALT: Alanine aminotransferase.

The negative control group (doxorubicin only) had an average ALT level of 441.62 \pm 30.11 U/L. The treatment group at a dose of 100 mg/kg BW had an ALT level of 383.8 \pm 17.38 U/L. The treatment group at a dose of 200 mg/g BW had an ALT value of 308.3 \pm 24.02 U/L. The treatment group at a dose of 400 mg/kg BW had an ALT value of 245.9 \pm 8.80 U/L. The mean value of ALT in the beetroot ethanol extract treatment group at

dose of 200 mg/kg BW was significantly different from negative control ($p < 0.05$; Table 1).

Effect of beetroot extract (BE) treatment on AST level

In this research, AST levels of rats blood were examined. The results of the levels obtained are presented in Table 2.

Table 2: Effects of BE treatment on AST Level

Group	AST level (U/L)					Mean \pm SD (U/L)
Normal control	65.3	70.2	64.5	51.5	57.2	61.74 \pm 7.37*
Negative control	145.4	165.2	134	155.3	158.2	151.62 \pm 12.14
BE 100 mg/kg BW	124.3	118.7	110.2	109.6	124	117.36 \pm 7.16*
BE 200 mg/kg BW	93.6	93.3	87	92.8	79.4	89.22 \pm 6.12*
BE 400 mg/kg BW	82.1	83.8	76.3	69.2	88.4	79.96 \pm 7.41*

Data expressed as mean \pm SD (n = 5). *Significant difference versus negative control group at $P < 0.01$. BE: Beetroot extract, BW: Body weight.

The negative control group (doxorubicin only) had an average AST value of 151.62 \pm 12.14 U/L. The treatment group dose 100 mg/kg BW had AST values of 117.36 \pm 7.16 U/L. The treatment group with a dose of 200 mg/kg BW had an AST value of 89.22 \pm 6.12 U/L. The treatment group at a dose of 400 mg/kg BW had an AST value of 79.96 \pm 7.41 U/L. Based on (Table 2), it was known that the mean AST value in the beetroot ethanol extract treatment group with a dose of 100 mg/kg BW was significantly different from the negative control ($p < 0.05$; Table 2).

Effect of beetroot ethanol extract on creatinine levels

In this research, creatinine levels from rats blood were examined. The results of the levels obtained are presented in Table 3.

Table 3: Effect of Beetroot Ethanol Extract on creatinine levels

Group	Creatinine levels (mg/dl)					Mean \pm SD (mg/dl)
Normal Control	0.23	0.27	0.28	0.25	0.24	0.26 \pm 0.01*
Negative Control	0.45	0.49	0.45	0.45	0.48	0.46 \pm 0.01
BE 100 mg/kg BW	0.38	0.45	0.47	0.43	0.45	0.43 \pm 0.03
BE 200 mg/kg BW	0.34	0.38	0.37	0.36	0.39	0.34 \pm 0.01*
BE 400 mg/kg BW	0.36	0.29	0.27	0.30	0.30	0.25 \pm 0.01*

Data expressed as mean \pm SD (n = 5). *Significant difference vs. negative control group at $P < 0.01$. BE: Beetroot extract, BW: Body weight.

The negative control group (doxorubicin only) had an average creatinine value of 0.46 \pm 0.01 mg/dl. The treatment group dose 100 mg/kg BW has creatinine value of 0.43 \pm 0.03 mg/dl. The treatment group at dose of 200 mg/kg BW has a creatinine value of 0.34 \pm 0.01 mg/dl. The treatment group at a dose of 400 mg/kg BW has a creatinine value of 0.25 \pm 0.01 mg/dl. Based on the table, it was known that the mean creatinine value in the beetroot ethanol extract treatment group with a dose of 200 mg/kg BW was significantly different from negative controls ($p < 0.05$; Table 3).

Effect of beetroot ethanol extract on urea

In this research, urea levels were examined in the blood of rats. The results obtained were presented in Table 4.

The negative control group (doxorubicin only) had an average urea value of 55.4 \pm 1.74 mg/dl. The treatment group at dose of 100 mg/kg BW had mean blood urea level of 48 \pm 1.41 mg/dl. The treatment group with a dose of 200 mg/kg BW had mean blood urea level of 45.2 \pm 0.97 mg/dl. The treatment group at dose of 400 mg/kg BW had mean blood urea level of 40.6 \pm 2.15 mg/dl. Therefore, the average urea in the treatment group of beetroot ethanol extract at a dose of 200 mg/kg BW was significantly different from negative controls ($p < 0.05$; Table 4).

Table 4: Effects of beetroot ethanol extract on urea level

Groups	Urea level (mg/dl)					Mean \pm SD (mg/dl)
Normal control	43	41	41	43	39	41.4 \pm 1.49*
Negative control	53	56	58	54	56	55.4 \pm 1.74
BE at dose of 100 mg/kg BW	46	48	50	49	47	48 \pm 1.41*
BE at dose of 200 mg/kg BW	47	45	45	44	45	45.2 \pm 0.97*
BE at dose of 400 mg/kg BW	38	42	43	42	38	40.6 \pm 2.15*

Data expressed as mean \pm SD (n = 5). *Significant difference versus negative control group at $P < 0.01$. BE: Beetroot extract, BW: Body weight.

Histological assessment

Figures 1 and 2 showed necrotic cells after treatment by large dose of doxorubicin. Microscopic examination on kidney and hepatic tissues showed no necrosis after treatment by beetroot extract at dose of 200 and 400 mg/kg BW. The result was in agreement with the biochemistry examinations, that the beetroot extract prevented necrosis in hepatic and kidney cells. The polyphenol content in beetroot might play important role in inhibiting hepatic and kidney necrosis induced by doxorubicin.

Elevation of oxidative stress by doxorubicin causes mitochondrial damage, lipid oxidation, and causes cell damage [16]. Cell damage can have an impact on degradation of organs such as liver and kidney tissues. It can increase liver function biomarkers ALT and AST as well as an increase in creatinine and BUN levels as markers of kidney function. This indicates that the induction of doxorubicin affects organs functions in the body. Table 5 showed that the group treated with beetroot extract at a dose of 200 mg/kg BW could improve serum levels of ALT and AST compared with negative controls ($p < 0.05$). The group treated with beetroot extract at a dose of 100 mg/kg BW also showed an improved effect on creatinine and urea values of rats compared with negative controls ($p < 0.05$). All parameters showed dose-dependent effect in the protective activity of beetroot extract on doxorubicin-induced toxicity.

Many studies had reported the role of medicinal plant in inhibiting hepatotoxic and nephrotoxic effects [17], [18], [19], [20]. The antioxidant content in beetroot extract activity might play a role in hepatoprotective and nephroprotective effects by inhibiting ROS. Beetroot contains marker compounds namely betanin which is a red pigment in beetroot [21], some phytochemical compound also found in beet root such as tannins, saponins, alkaloids, flavonoids, terpenoids and steroids. Betanin has an

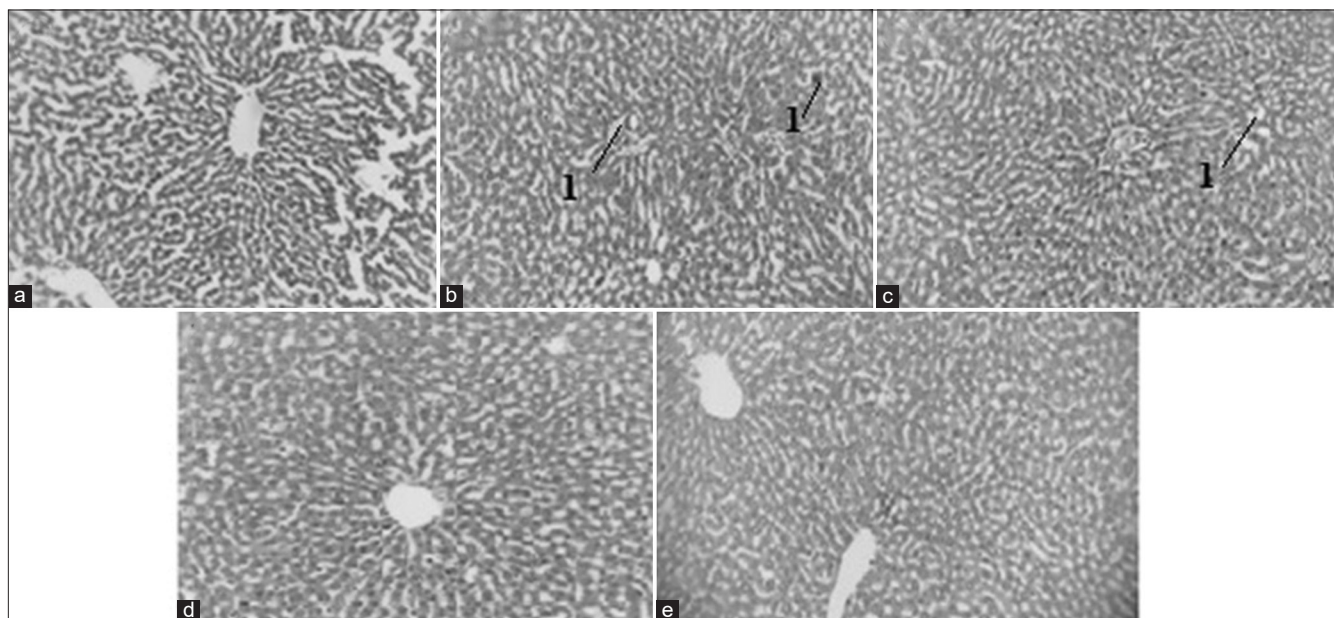


Figure 1: Microscopic examination (10×10) of (a) liver of normal control rat; (b) liver of negative control rat; (c) liver after treatment with beetroot extract at 100 mg/kg body weight (BW); (d) liver after treatment with beetroot extract at 200 mg/kg BW; (e) liver after treatment with beetroot extract at 400 mg/kg BW; (1) necrotic hepatocytes

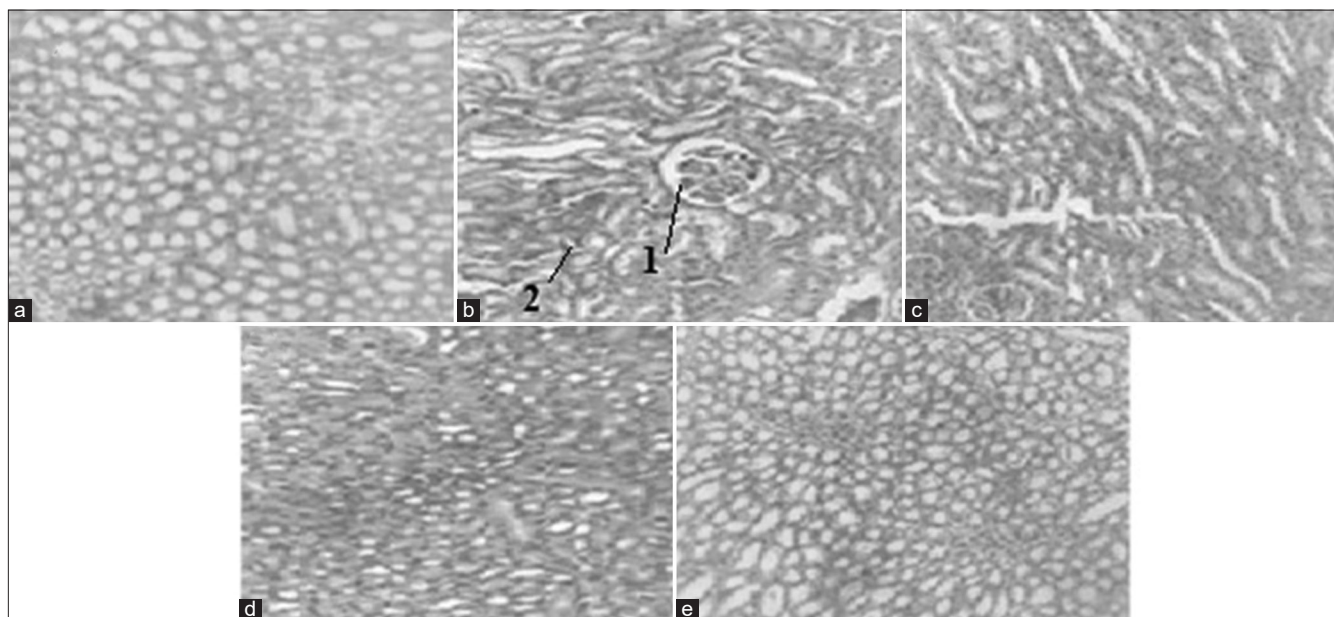


Figure 2: Microscopic examination (10×10) of (a) Kidney of normal control rat; (b) Kidney of negative control rat (c) Kidney after treatment with beetroot extract at 100 mg/kg body weight (BW); (d) Kidney after treatment with beetroot extract at 200 mg/kg BW; (e) Kidney after treatment with beetroot extract at 400 mg/kg BW; (1) Glomerulus atrophy; (2) Necrotic

antioxidant activity [22]. Betanin is a red-violet pigment that is a heterocyclic compound found in beetroot (*B. vulgaris* L.) [23], [24]. The antioxidant activity of betanin is due to the presence of a hydroxyl and cyclic amine groups that are hydrogen and electron donors, it has an efficacy to stabilize the reactive species [25]. In addition, phytochemical contents in beetroot were a powerful antioxidant that can prevent ROS free radical reactions caused by doxorubicin.

The antioxidant compounds present in beetroot in the form of betanin and also the content of

flavonoids and tannins which are polyphenols play roles in protecting liver and kidney against oxidative stress induced by doxorubicin. These results were also in line with research conducted by El Gamal *et al.* (2014), and Agarwal *et al.* (2006) who concluded that beetroot extract protects the kidney function of mice in gentamicin-induced nephrotoxicity and it also can protect the liver function of mice induced by CCl₄ [26], [27]. Based on histological analysis, supplementation of beetroot extracts which are rich in antioxidants can provide protection against oxidative stress reactions caused by doxorubicin.

Conclusion

Beetroot ethanol extract has hepatoprotective and nephroprotective activities in rats that are induced by doxorubicin and it showed dose-dependent effects.

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