

Nephroprotective effect of mengkudu (*Morinda citrifolia*) on rats induced by doxorubicin

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ABSTRACT

Chronic kidney disease in the world is currently experiencing an increase and become a serious health problem. Doxorubicin clinical efficacy is hampered by dose-related organotoxic (heart, liver, and kidney) potential. The purpose of this study was to determine the nephroprotective activity of mengkudu fruit ethanol extract against the rats induced by doxorubicin. Mengkudu fruit ethanol extract was obtained by maceration. Nephroprotective activity test is done by measuring urea and creatinine. Animals were induced with doxorubicin (DOX) 5 mg/kgbw on day 1, 7, 14 and 20th. Administration of mengkudu extract 100 mg/kgbw, 300 mg/kgbw, and 500 mg/kgbw given from day 1 to day 20 and on the 21st day blood serum levels of urea and creatinine. Mengkudu dose of 100 mg/kg BW, 300 mg/kgbw and 500 mg/kgbw have nephroprotective activity against male rats induced by doxorubicin. The effective dose of mengkudu as nephroprotective is at a dose of 500 mg/kgbw with a serum creatinine level of 0.570 ± 0.030 mg/dl and a serum urea level of 28.333 ± 6.210 mg/dl which shows a significant difference ($p < 0.05$) of negative controls and not significantly different ($p > 0.05$) from positive control (Vitamin E). In the positive control group and the administration of mengkudu 500 mg/kgbw, the kidney tissue appeared normal. In the treatment group, mengkudu 500 mg/kgbw did not occur kidney tissue damage because mengkudu was able to repair kidney damage due to doxorubicin induction.

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INTRODUCTION

Chronic kidney disease in the world is currently experiencing an increase and become a serious health problem, research results Global burden of disease in 1990 chronic kidney disease was the 27th leading cause of death in the world and an increase

to 18th in the year 2010. More than 2 million people in the world get treatment with dialysis or kidney transplants and only about 10% actually experience the treatment, and ten percent of the world's population experiences chronic kidney disease and millions die every year because they do not have access to treatment [1].

According to estimates from the World Health Organization (WHO) in 2015, cancer is the first or second leading cause of death before the age of 70 in 91 of 172 countries and ranks third or fourth in 22 additional countries. Cancer incidence and mortality are growing rapidly throughout the world. The reasons are complex but reflect aging and population growth, as well as changes in the prevalence and distribution of major cancer risk factors, some of which are related to socio-economic development. With rapid population growth and aging throughout the world, the increasing prominence of can-

cer as a leading cause of death reflects in part a sharp decline in mortality due to stroke and coronary heart disease, relative to cancer, in many countries. The extent to which the position of cancer as a cause of early death reflects the level of national social and economic development [2].

Radiation and chemotherapy are treatments that are widely used for cancer. Despite their antitumoral effects in controlling primary and metastatic tumors, both therapeutic modalities can produce toxicity in normal tissue and often, associated side effects outweigh clinical benefits and worsen the patient quality of life [3].

Anthracycline doxorubicin (Dox) is a very effective anti-neoplastic agent, which intercalates in DNA and inhibits topoisomerase II. DOX is one of the most common systemic treatments to improve some cancers in adults and children alike, including hematologists and solid tumors. Unfortunately, Dox's clinical efficacy is hampered by dose-related organotoxic (heart, liver, and kidney) potential, which can be life-threatening. Several cytotoxic mechanisms are involved in the pathogenesis of Dox-induced nephrotoxicity by decreasing the glomerular filtration rate that occurs in 15-30% of patients. Various mechanisms contribute to renal dysfunction after Dox exposure including tubular epithelial cell toxicity, vasoconstriction in renal microvasculature, and increase expression of proinflammatory cytokines [4]. However, a large amount of evidence indicates that oxidative stress induced by Dox remains the basis, as evidenced by reactive oxygen species (ROS) induces oxidative damage such as lipid peroxidation and protein, and over renin activity that produces angiotensin II. Angiotensin II, the main effector of the renin-angiotensin system (RAS), has been reported to have an important role in the pathogenesis of several cardiovascular and kidney injuries [5].

Besides, nephrotoxicity is a common and severe side effect due to oxidative stress and Dox produces drastic cellular negligence in the kidneys, including focal necrosis and fibrosis in the cells of the kidney organs. Renal fibrosis occurs due to inflammation of the tubular and glomerular epithelium. This is indicated by the number of widening junction cells [6]. Dox-induced nephrotic syndrome is characterized by proteinuria and hypoalbuminemia. At present, there are no specific and effective therapeutic agents to avoid organ toxicity associated with Doxorubicin. Thus, studies of compounds that can increase the index of chemotherapy and radiotherapy that do not have side effects on healthy tissue and without affecting its anti-neoplastic effects are

urgently needed [7, 8].

Vitamin E is an antioxidant that can reduce the effects of tissue damage caused by free radicals so that vitamin E is useful in the treatment of neurological, cardiovascular, urinary tract and malignant diseases such as tumors and cancer [9]. The nephroprotective effect of Vitamin E is by protecting cells from free radicals or oxidative stress [10]. Tocotrienol is a natural component of Vitamin E in addition to tocopherols which are fat-soluble antioxidants that protect cell membranes from oxidative damage. Tocotrienol and tocopherol are combination ingredients to reduce the effects of free radicals, inhibit cancer growth, nephroprotective, and premature aging [11].

Mengkudu (*Morinda citrifolia*) is an important plant that has many phytochemicals, which play a very important role in the treatment and prevention of various diseases. The content of macronutrient nutrients such as carbohydrates (Oligo and polysaccharides) and micronutrients such as vitamin C, caprylic acid, niacin (Vitamin B3), iron, potassium, vitamin A, calcium, and sodium as well as alkaloids and flavonoids in mengkudu can work as a protector for kidney disorders and the content of amino acids such as alanine, arginine, cysteine, phenylalanine, glycine, isoleucine, leucine, lysine, methionine, proline, tyrosine, tryptophan, and valine. It has many medical properties such as preventing all types of cancer, reducing heart disease, the role of blood pressure, increasing endurance, controlling diabetes mellitus, reducing asthma, good antioxidants, strengthening neurons due to a good nervous system, controlling cholesterol levels that reduce weight body and get better skin. Mengkudu is one of the herbal formulations of *Morinda citrifolia* that removes calcium oxalate that is not soluble in water and converts it to water-soluble calcium. *M. citrifolia* parts such as fruit, leaves and root extracts remove lipids from proven animal models. Now it will be excreted in the urine easily and prevents the formation of stones. This is a herbal formulation and therefore does not cause side effects [12].

Based on the above background chemotherapy drug such as doxorubicin which cause nephrotoxicity, and antioxidant content in mengkudu fruit which is very beneficial for human health. This study aims to determine the nephroprotective effect of mengkudu ethanol extract by measuring serum urea and creatinine levels as biomarkers of kidney function.

MATERIALS AND METHOD

Material

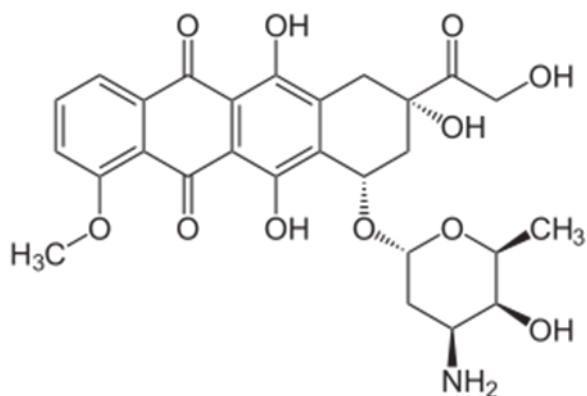


Figure 1: Structure of doxorubicin

Surgical instruments, laboratory glassware, aluminum foil, blender, porcelain cup, desiccator, incubator, slide glass, cover glass, porcelain crucible, drying cabinet, microtube, light microscope, analytical balance, oral sonde, electric oven, bathwater, tube clamps, test tube racks, rotary evaporators, centrifugation, a set of moisture determination devices, UV spectrophotometers, injection syringes, furnaces, test tubes, animal scales, Spectrophotometers are able to read absorbance numbers at 340 nm, Accurate plumbing devices, Interval Timer, Cuvettes and / or Test Tubes, Mixers (Vortex type), constant temperature Bath, or heating block set at 37°C or temperature controlled, Doxorubicin, NaCl, 10% formalin, chloroform, Carboxy Methyl Cellulose- Sodium (CMC-Na), Vitamin E, Urea reagent, Creatinine reagent, liquid paraffin, toluene, and acetone.

Animals

An animal used in research is a rat (*Rattus norvegicus*) Wistar male 150 – 200 g. Before the study began, animal test adjusted for one week with the condition of the room temperature (22-25°C), under the cycle of 12 hours light/ dark, given the food and the drinking water ad libitum. Ethics Commission from health and science was from University of Sumatera Utara. Animal ethical approval committee number: 0525/KEPH-FMIPA/2019.

Preparation of ethanol mengkudu extract

Mengkudu fruit is separated from the seeds, the flesh and the skin are taken. Then chopped and dried in a drying cabinet for 3 days. The making of mengkudu fruit ethanol extract was done by maceration with 96% ethanol solvent. A total of 500 grams of mengkudu powder was put into a glass container, 96% of ethanol was added as much as 3.75 L, cover, leave for 5 days protected from light while stirring frequently, squeeze, wash the dregs with enough liquid to obtain 4 L. Transfer to a closed vessel, leave in

a cool place, protected from light for 2 days. Encapsulated or filtered. The results obtained are concentrated with the rotary evaporator until most of the solvent is evaporated and the evaporation process is continued on the water bath until a thick extract is obtained (mengkudu fruit ethanol extract).

Phytochemical screening of ethanol mengkudu extract

Phytochemical screening of ethanol mengkudu extract method consisted of identification of phenol, steroids/terpenoids, saponins, flavonoids, tannin and alkaloids.

In vivo test nephroprotective effect of mengkudu

In vivo tested in an experiment by using 25 Wistar rats (*Rattus norvegicus*) male and weight 150 g - 200 g, as many as 24 and divided into 6 groups and each group consisted of 4 rats,

Normal

Suspension Na-CMC.

Negative control

Wistar rats (*Rattus norvegicus*) male induced by doxorubicin 15 mg/kgbw.

Positive control

Wistar rats (*Rattus norvegicus*) male induced by doxorubicin 15 mg/kgbw + Vitamin E 1%.

Group 1

Wistar rats (*Rattus norvegicus*) male induced by doxorubicin 15 mg/kgbw + 100 mg/kgbw.

Group II

Wistar rats (*Rattus norvegicus*) male induced by doxorubicin 15 mg/kgbw + 300 mg/kgbw.

Group III

Wistar rats (*Rattus norvegicus*) male induced by doxorubicin 15 mg/kgbw + 500 mg/kgbw.

Induction of kidney damage was done by using doxorubicin with an accumulative dose of 15 mg/kg for 21 days, with 5 mg/kg once a week. Before the treatment of male Wistar rats (*Rattus norvegicus*) was adapted for 14 days then continued with doxorubicin induction and treatment of experimental animals for 21 days with extract of mengkudu administration with 100 mg/kgbw, 300 mg/kgbw, and 500 mg/kgbw dose. Then on the last day, the treatment of male Wistar rats (*Rattus norvegicus*) was fasted for 18 hours, performed surgery on the test animals. Wistar rats (*Rattus norvegicus*) male fasted for about 18 hours (not given food, but still given a drink). Male Wistar rats (*Rattus norvegicus*) were anesthetized with ketamine at a dose of 70 mg/kg

bb i.v. Male Wistar rats (*Rattus norvegicus*) are then tethered to the board on all four limbs. The chest cavity was dissected and 3 ml of blood in the heart was taken using a 5 ml syringe. The blood is then transferred in a blood tube. Then the blood is centrifuged for 10 minutes at a speed of 3000-4000 rpm to produce 2 layers, namely serum /supernatant and its sediment. The serum layer is then taken using a 1 ml syringe, stored in a microtube and stored in a refrigerator at -4°C. Blood serum is used for the examination of total urea and creatinine [13].

Determine of urea and creatinine

Measurement of the levels of urea and creatinine is performed by following the method of Bhavani *et al.* [8]. As many as 50 μ l samples and 500 μ l of Urea reagent/Creatinine mixed in a test tube. Then the initial absorbance read after 1 minute at a wavelength of 340 nm. Next, the absorbance was measured again after 1, 2, and 3 minutes [14].

Statistical analysis

Test analysis was carried out by using one-way analysis of variance (ANOVA) followed by Post Hoc Test using the Tukey HSD test. $P < 0.05$ was considered as statistical significance and also use IBM SPSS 20.

RESULT AND DISCUSSION

Authentication of plant

The results of the identification of plants carried out by Rosnizal (2019) at the Medanese Herbarium (MEDA) the University of North Sumatra, the fruit used in this study was Mengkudu (*Morinda citrifolia*).

Phytochemical result

The results of phytochemical screening qualitatively in mengkudu extract are shown in Table 1.

Table 1: Results of phytochemical screening of mengkudu extract

Chemical Component	Result
Tanin	+
Saponin	+
Flavonoid	+
Steroid	+
Glikosida	+
Alkoloid	+

Phytochemical screening of ethanol mengkudu showed the positive result of flavonoids, tannins, saponins, glycosides, alkaloid, and steroids.

Mengkudu (*Morinda citrifolia*) is a medicinal plant that can be used for the treatment of various dis-

eases including cancer, infections, arthritis, diabetes, asthma, hypertension, and injuries. Another research stated that the mengkudu fruit and leaf parts have the ability as natural antioxidants. Antioxidant activity has a positive linear relationship with phenol content in mengkudu fruit extract. Phenolic compounds, especially phenolic acids and flavonoids, are natural antioxidants in fruits, vegetables, and other plants. In this study, determining the most active fraction of mengkudu fruit and leaf extracts through testing of DPPH free radicals, then determining the total phenol content, antioxidant activity, and identification of the antioxidant compounds through phytochemical tests. The determination of the antioxidant activity of the mengkudu extract fraction in this study is the DPPH method. This method is an antioxidant analysis method based on the capture of free radicals with DPPH as free radicals and one of the spectro-photometric methods that are easy and is widely used for the determination of antioxidant activity [15].

Creatinine level

In this study, serum creatinine from rat blood was examined. Creatinine serum examination was performed at Medan Regional Health Laboratory. The results of serum creatinine obtained can be seen in Table 2.

Table 2: Creatinine level

No.	Doses	Mean Creatinine \pm SD (mg/dl)
1.	Normal	0.376 \pm 0.025
2.	Negative control	1.136 \pm 0.077
3.	Positive control	0.483 \pm 0.020
4.	Group I	0.876 \pm 0.020
5.	Group II	0.746 \pm 0.015
6.	Group III	0.570 \pm 0.030

The data presented in the form of Mean \pm SD. Data obtained is based on the results of statistical tests, serum creatinine levels in the negative control group CMC Na 0.5% had a significant difference ($p < 0.05$) with other treatment groups. The serum creatinine levels in the positive control group vitamin E were not significantly different ($p > 0.05$) from the normal group, and were significantly different ($p < 0.05$) with mengkudu 100, 300, 500 mg/kgbw. The serum creatinine levels in the mengkudu treatment group 100 mg/kgbw did not have a significant difference ($p > 0.05$) to the mengkudu 300 and 500 mg/kgbw treatment groups and were significantly different ($p < 0.05$) in the normal group treatment group, negative groups, and

positive groups. The serum creatinine levels in the mengkudu 300 mg/kgbw group had a significant difference ($p < 0.05$) in the normal group, the negative group, and the positive group. The serum creatinine levels of the mengkudu treatment group 100 mg/kgbw and mengkudu 300 mg/kgbw have a significant difference ($p < 0.05$) with the normal and positive control groups. The serum creatinine levels in the mengkudu 500 mg/kgbw group had a significant difference ($p < 0.05$) in the negative group, and the positive group.

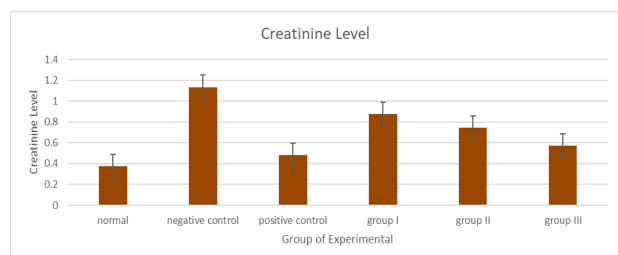


Figure 2: Creatinine level

Based on Table 2 it is known that the average serum creatinine value for the negative group was 1.136 mg/dl. Levels in the normal group are still in the maximum threshold, which is between 0.3-1.0 mg/dl.

The positive control group had an average serum creatinine of 0.483 mg/dl while the mengkudu treatment group of 100 mg/kgbw had an average serum creatinine value of 0.876 mg/dl. The mengkudu 300 mg/kgbw treatment group had an average creatinine serum value of 0.746 mg/dl, and the average creatinine serum value for the 500 mg/kgbw mengkudu treatment group was 0.570 mg/dl.

Based on the Table 2, it is known that the average serum creatinine in the largest treatment group is 0.876 mg/dl in the administration of mengkudu 100 mg/kgbw and the lowest mean serum creatinine in the administration of mengkudu 300 mg/kgbw. Also, it can be seen that there is a decrease in serum creatinine levels with increasing mengkudu doses. The average bar chart of serum creatinine measurements in male rats can be seen in Figure 2.

This study was conducted to determine the effect of mengkudu administration on serum creatinine levels and kidney organ histology in male rats due to the administration of doxorubicin with toxic doses. Mengkudu is given in various doses to find out mengkudu can neutralize kidney damage due to doxorubicin toxic doses with indicators of decreased serum creatinine levels and histology of rat kidney organs.

In general, the biological effects caused by the use of anthracycline doxorubicin are the occurrence of

apoptosis, necrosis, and autophagy [16]. The mechanism of action of doxorubicin can be explained by the use of doxorubicin distributed intravenously in the body within 3-5 minutes and can circulate up to 24-36 hours in the bloodstream. Doxorubicin and the main metabolites of doxorubicin are bound by plasma proteins, then enter cells through passive diffusion with high affinity to bind to cytoplasmic proteasomes. Oxygen-free radicals produced during doxorubicin activity have toxic effects on the liver tissue which are equipped with a detoxification mechanism of the bad species instead which tend to have toxic effects on the liver. The unique dose distribution of doxorubicin decreases the cytochrome P-450 and glutathione content in the liver, where it is known that glutathione is a protective hepatocyte isolated from toxicity. Two ways of free radical formation by doxorubicin, the first pathway causes the formation of semiquinone free radicals by the formation of several doxorubicin semi-inhibitors. In the presence of oxygen, the redox cycle of Dox-derived quinone produces superoxide radical semiquinone derivatives. In the second pathway, the free radical doxorubicin is derived from a non-enzymatic mechanism involving reactions with iron. For example, Fe^{3+} reacts with doxorubicin in a redox reaction which then the iron atom receives electrons and the free radical Fe^{2+} doxorubicin complex is produced. This Fe^{2+} doxorubicin complex can reduce oxygen to hydrogen peroxide and other active oxygen species. As a result of oxidative metabolism doxorubicin will produce superoxide ion radicals, H_2O_2 radicals and hydroxyl [17].

Creatinine is a muscle breakdown product that indicates impaired kidney function if the levels exceed normal limits. Serum creatinine is a strong indicator of kidney function and its concentration is relatively constant from day to day [18].

Urea level

The results of serum urea obtained can be seen in Table 3.

Table 3: Urea level

No.	Doses	Mean Urea \pm SD (mg/dl)
1.	Normal	19.333 \pm 1.527
2.	Negative control	36.333 \pm 1.527
3.	Positive control	21.667 \pm 1.527
4.	Group I	32.000 \pm 1.000
5.	Group II	31.000 \pm 1.000
6.	Group III	28.333 \pm 6.210

The data presented in the form of Mean \pm SD. Data

obtained is based on the results of statistical tests, the serum urea level of the negative control group CMC Na 0.5% had a significant difference ($p < 0.05$) with other treatment groups. The serum urea level of the positive control group Vitamin E did not differ significantly ($p > 0.05$) from the normal group, and it was significantly different ($p < 0.05$) with the negative group, mengkudu 100, 300 and 500 mg/kgbw. The serum urea level of the mengkudu treatment group 100 mg/kgbw did not have a significant difference ($p > 0.05$) to the mengkudu 300 and 500 mg/kgbw treatment groups and was significantly different ($p < 0.05$) to the normal group, negative, and positive groups. The serum urea level of the mengkudu 100 mg/kgbw group had a significant difference ($p < 0.05$) in the normal group, the negative group, and the positive group. The serum urea level of the mengkudu treatment group 100 mg/kgbw, 300 mg/kgbw and mengkudu 500 mg/kgbw had significant differences ($p < 0.05$) with the normal, negative and positive control groups.

Based on table Table 3 it is known that the average serum urea value for the negative group is 36.333 mg/dl. Levels in the negative group are in the abnormal range of serum urea, which is between 11.1-19.9 mg/dl [18].

The normal group had an average serum urea value of 19.333 mg/kgbw, the positive control group had average serum urea of 21.667 mg/dl while the mengkudu treatment group of 100 mg/kgbw had an average serum urea value of 32.000 mg/kg dl. The mengkudu treatment group 300 mg/kgbw has an average serum urea value of 31.000 mg/dl, as well as the average urea serum value for the mengkudu treatment group 500 mg/kgbw of 28.333 mg/dl.

Based on the table Table 3 it is known that the average serum urea in the largest treatment group is 32.000 mg/dl at the administration of mengkudu 100 mg/kgbw and the smallest average serum urea at 28.333 mg/dl at the giving of mengkudu 500 mg/kgbw. Besides, it can be seen that there is a decrease in serum urea levels with increasing mengkudu doses. The average bar chart of the measurement of serum urea in male rats can be seen in Figure 3.

This study was conducted to determine the effect of mengkudu administration on serum urea and creatinine in male rats due to doxorubicin induction. Mengkudu is given in various doses to find out mengkudu can neutralize kidney damage due to doxorubicin induction with indicators of decreased serum urea levels and histology of rat kidney organs [19].

Hirazumi *et al.* [20] suggested that the increase in

urea in the blood can be caused by several conditions, including,

- Increased tissue protein catabolism is accompanied by a negative nitrogen balance.
- Excessive breakdown of blood protein.
- Reduction in urea excretion due to decreased glomerular filtration rate.

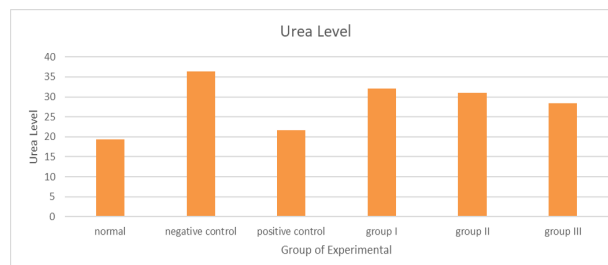


Figure 3: Urea level

The determination of urea levels in serum reflects the balance between production and excretion. In the United States, the result of the determination is referred to as blood urea nitrogen. The urea is one of the common signs used to estimate glomerulus filtration rate (GFR), but urea examination is only as a supporting examination for several reasons, some of which are due to urea levels not only influenced by kidney function but also by its production which comes from the intake of protein and urea which is also reabsorbed by the tubules [21]. The explanation above proves that mengkudu containing polyphenol compounds can function as a nephroprotective. The results obtained are by previous studies conducted by Kumar *et al.* [22] which in his research said that the administration of mengkudu has high antioxidants so that it can be used as a doxorubicin-induced nephroprotective.

Hydropic degeneration or swelling is an early stage of necrosis characterized by swollen hepatocytes, where there is a pale, round-shaped vacuole caused by paralysis of ion pump activity in the plasma membrane so that it is unable to maintain the balance of ions and liquids [23].

Oxidative stress caused by doxorubicin activates apoptotic signals in cardiomyocytes, through their extrinsic and intrinsic apoptotic pathways. A description of all the apoptotic pathways involved in doxorubicin-induced cardiotoxicity can be seen in the picture which states that doxorubicin can induce apoptotic mechanisms that occur indirectly involving the production of ROS and oxidative stress, and apoptosis itself also produces free radicals. Proapoptotic protein production has a different role in this process [24]. This protein as a molecular

companion acts to stabilize the proteins involved in anti-apoptosis and signify it can prevent dephosphorylation and expression.

CONCLUSIONS

Mengkudu dose of 100 mg/kgbw, 300 mg/kgbw and 500 mg/kgbw have nephroprotective activity against male rats induced by doxorubicin. The effective dose of mengkudu as nephroprotective is at a dose of 500 mg/kgbw with a serum creatinine level of 0.570 ± 0.030 mg/dl and a serum urea level of 28.333 ± 6.210 mg/dl which shows a significant difference ($p < 0.05$) of negative controls and not significantly different ($p > 0.05$) from positive control (Vitamin E). In the positive control group and the administration of mengkudu 500 mg/kgbw, the kidney tissue appeared normal. In the treatment group, mengkudu 500 mg/kgbw did not occur kidney tissue damage because mengkudu was able to repair kidney damage due to doxorubicin induction.

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Conflict of Interest

The authors declare that they have no conflict of interest.

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