Research Article

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# Antioxidant activity and nephroprotective effect of *Lansium parasiticum* leaves in doxorubicin-induced rats

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**ABSTRACT**: Doxorubicin is an important drug, especially in the treatment of cancer. But the effectiveness of its use is inseparable from its side effects, such as nephrotoxicity. This study aimed to examine the protective effect in doxorubicin-induced rats of Extract Ethanol of *Lansium parasiticum* leaves (EELP). The antioxidant activity of EELP was identified using the DPPH method and traced the total phenol content using the Folin-Ciocalteu method and total flavonoids using the colorimetry method. Oxidative stress and renal injury induced in doxorubicin treated rats were proved by the significant elevation of urea and creatinine and alteration in oxidative stress markers [MDA and GSH levels]. Histopathology of organs was examined under a microscope to see the damage that occurs in the tissue. The measurement results of antioxidant activity showed that EELP had a strong activity with an $IC_{50}$ value of 14.8±0.7 µg/mL, 107.5±0.8 µg GAEs/mg extract for phenol content, and 33.6±0.3 µg quercetin/mg extract for flavonoid content. EELP was able to reduce MDA, urea, creatinine and increase GSH level. Observation of kidney tissues revealed a protective effect of EELP. This was characterized by a reduction in the type of damage that occurs in the kidney tissue of doxorubicin-induced rats. This study suggests that EELP through its antioxidant properties has a protective effect against doxorubicin-induced nephrotoxicity.

**KEYWORDS**: Nephrotoxicity; Doxorubicin; *Lansium parasiticum*; Oxidative stress

## 1. INTRODUCTION

Doxorubicin is an active compound that belongs to the anthracycline class and has been used as an anticancer drug mainly in breast cancer, lung cancer, and liver cancer [1]. Doxorubicin works by changing DNA function, inhibiting topoisomerase II enzyme activity, and disrupting the flow properties of cell membranes [2]. Therefore, the effectiveness of this drug has never been separated from its side effects. For this reason, doxorubicin is considered as a chemotherapy drug [3]. Doxorubicin not only causes damage to cancer cells, but also damages normal cells, such as heart cells, liver cells, and kidney cells [4–6].

Doxorubicin-induced oxidative damage can also cause nephrosis progression [7]. Several studies have shown that an increase in oxidative stress and free radicals due to the use of doxorubicin triggers nephrotoxicity. The results of research on male rats showed an increase in the value of malondialdehyde (MDA) from the kidney. In addition, doxorubicin caused a decrease in glutathione (GSH) values [8–10]. This results in weakened cellular defense against free radical attacks. Therefore, a compound with the ability to protect the kidneys from damage caused by doxorubicin is needed [11].

*Lansium parasiticum* is a plant that belongs to the Meliaceae family, growing up to 20 meters with a stem diameter of 35-40 cm [12]. For information, *Lansium parasiticum* thrives in tropical climates, such as Southeast Asia, especially Indonesia. It was reported that this plant has antimalarial, antimutagenic, and anticancer properties [13]. Its pharmacological activity cannot be separated from the content of active compounds in this plant. It was reported that this plant is rich in terpenoid compounds, phenolic compounds, and saponins [14]. This compounds were reported to have antioxidant activity that can suppress oxidative stress conditions, prevent an increase in lipid peroxidation, and trigger intracellular antioxidants, thereby providing a nephroprotective effect [15,16].

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## 2. RESULTS AND DISCUSSION

### 2.1 Antioxidant activity, total phenolic and flavonoid content

The antioxidant activity of EELP was determined using the DPPH method. The $IC_{50}$ value is used as a parameter to describe the antioxidant activity of the test material. From the test results, the sample $IC_{50}$ value is 14.8±0.7 µg/mL, lower than quercetin, which is 9.6±0.3 µg/mL which can be seen in Table 1. The $IC_{50}$ value is expressed as the ability of EELP to reduce 50% of free radicals formed from DPPH reagents. It was reported that the $IC_{50}$ value < 50 µg/mL indicated that the sample had very strong antioxidant activity [17].

**Table 1.** Antioxidant activity ($IC_{50}$), total phenolic and flavonoid content of *Lansium parasiticum* leaves extract

| Sample | Antioxidant activity | Phenolic content | Flavonoid content |
|---|---|---|---|
| | $IC_{50}$ (µg/mL)[a] | (µg GAEs/mg extract)[b] | (µg quercetin/mg extract)[c] |
| EELP | 14.8±0.7 | 107.5±0.8 | 33.6±0.3 |
| Quercetin | 9.6±0.3 | *NT* | *NT* |

[a]$IC_{50}$ values represent the means ± S.E.M. of three parallel measurements ($p < 0.05$).
[b]GAEs, gallic acid equivalents, and the values represents the mean ± S.E.M ($p < 0.05$).
[c]Quercetin equivalents, and the values represents the mean ± S.E.M ($p < 0.05$).
*NT*: not tested

The content of phenols and flavonoids in the sample affects the antioxidant properties of the EELP. Phenol and flavonoid compounds have a linear contribution with antioxidant activity, so the higher the levels of phenol and flavonoid the better the antioxidant effect [18–20]. In this study, the total phenol and flavonoid content of EELP were 107.5±0.8 µg/mL and 33.6±0.3 µg/mL, respectively. As antioxidants, phenolic compounds including flavonoids work by reducing free radicals. This ability is highly dependent on the number of hydroxy groups of the compound [21].

### 2.2 Effect of extract on malondialdehyde (MDA) and Glutathione (GSH) levels

Doxorubicin has the potential of causing nephrotoxicity. This is due to its ability to induce reactive oxygen species (ROS) production, this condition is known as oxidative stress [22]. ROS damage tubular cells proximal, endothelial, basement membrane, mesangial cells, and visceral glomerular cells [23]. Malondialdehyde (MDA) is a marker of oxidative stress, where high MDA values have an impact on cell damage and are often accompanied by a decrease in natural antioxidants, such as glutathione (GSH) [24,25]. Based on the results of the study, EELP was able to suppress the increase in MDA and trigger GSH values in the kidneys of rats induced by doxorubicin. The results of a decrease in MDA value and an increase in GSH can be seen in Figure 1.

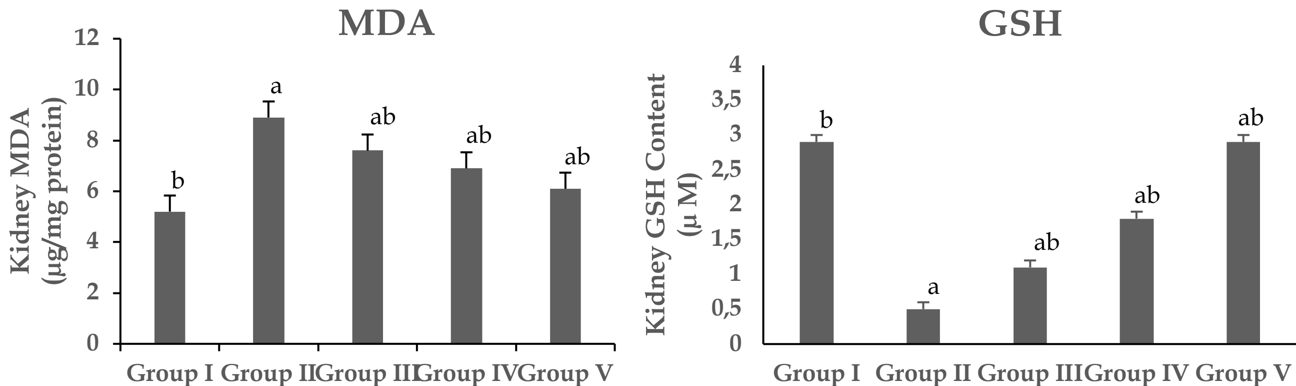


**Figure 1.** Effect of EELP on MDA and GSH levels in doxorubicin-induced. a: significantly different with group I ($p<0.05$); b: significantly different with group II ($p<0.05$). Statistical analysis was carried out by SPSS 25 using one-way ANOVA, *post hoc tukey* test.

Based on Figure 1, there was a decrease MDA value in group III, group IV, and group V when compared to group II with $p<0.05$. Group V was the group that was more effective in reducing MDA levels


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than groups III and IV with values of 6.1±0.1 µg/mg, 6.9±0.5 µg/mg, and 7.6±0.2 µg/mg, respectively. This is supported by data on the increase in GSH levels from group III, group IV, and group V when compared to group II with GSH levels in each group being 1.1±0.1 µM, 1.8±0.1 µM, 2.9±0.2 µM, and 0.5±0.1 µM with p <0.05. Malondialdehyde is a product lipid peroxidation which is an aldehyde reactive is a reactive electrophile species which causes toxic stress on cells and form covalent protein products known as advance lipoxidation end products [26]. In the body, these compounds act as free radicals that will damage cell function. The ability of EELP as an antioxidant will suppress the amount of MDA formed to protect body cells against oxidative damage. The decrease of MDA level cause the function of glutathione S-transferase to return to normal which has an impact on increasing GSH values [27].

### 2.3 Effect of extract on urea and creatinine levels

Kidney damage causes an increase in the amount of urea in the blood. Urea is a waste product, the result of protein metabolism in the liver that must be removed from the body [28]. Loss of kidney function will cause a buildup of urea in the body which can have a toxic effect. The same is true for creatinine, which is used as a sign of kidney damage [29]. This compound is a product of endogenous metabolism, synthesized in skeletal muscle, liver, and kidneys. Another very specific role of creatinine is to assess the function of the glomerulus [30]. The measuring results of urea and creatinine levels from doxorubicin-induced rats can be seen in Figure 2.

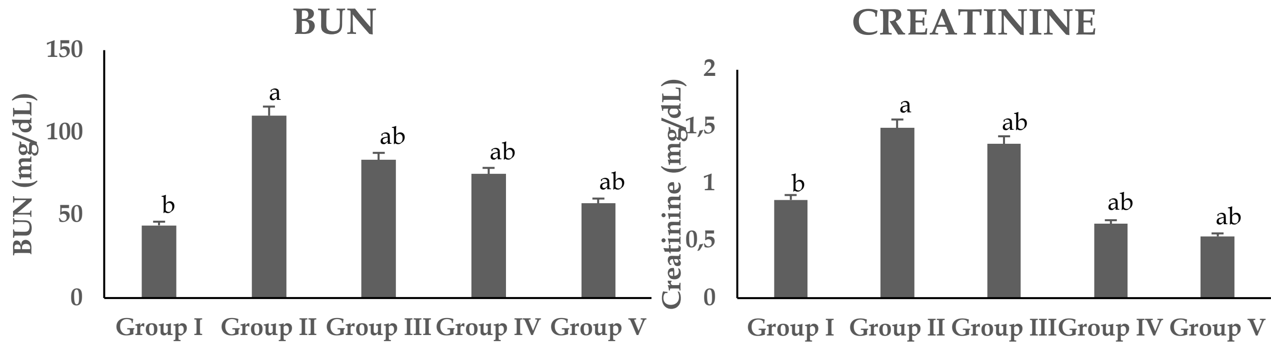


**Figure 2.** Effect of EELP on BUN and Creatinine levels in doxorubicin-induced. a: significantly different with group I (p<0.05); b: significantly different with group II (p<0.05). Statistical analysis was carried out by SPSS 25 using one-way ANOVA, *post hoc tukey* test.

Administration of doxorubicin in rats caused an increase in BUN and creatinine values with values of 110.33±1.53 µg/dL and 1.49±0.07 µg/dL, respectively (p<0,05). This indicates that the rat kidney organ is damaged. EELP can reduce BUN and creatinine values from experimental animals. It can be seen that the higher the dose of EELP given, the higher the decrease in BUN and creatinine [31]. The most effective group in reducing the risk of kidney damage was group V with BUN and creatinine values of 57.33 ± 1.52 µg/dL and 0.54 ± 0.01 µg/dL, (p<0,05). Urea and creatinine are waste products that will be excreted through the kidneys. Glomerular damage due to doxorubicin administration will inhibit the excretion of urea which can worsen kidney performance [32]. The same is true for creatinine, where the main elimination of creatinine occurs through the kidneys. A two-fold increase in serum creatinine level indicates a 50% decrease in renal function, as well as A threefold increase in serum creatinine level reflects the decreased kidney function by 75% [33].

### 2.4 Effect of extract on histopathology of kidney tissue in doxorubicin treated rat

Doxorubicin is a chemical drug that is widely used in the treatment of cancer. The use of doxorubicin has been reported to cause kidney damage [34]. The mechanism of the toxicity of doxorubicin is mediated by metabolite conversion doxorubicin to doxorubicinol which involves various enzymes, including carbonyl reductase. It was explained that the main mechanism of doxorubicin toxicity was due to its interaction with iron and the formation of reactive oxygen species (ROS) that damage cell macromolecules [35]. Kidney damage can be observed directly using histopathological techniques. Kidney organs of rats induced by doxorubicin were prepared using hematoxylin-eosin solution and observed under a microscope [36]. The results of hematoxylin-eosin treatment in rat kidneys are shown in Figure 3.


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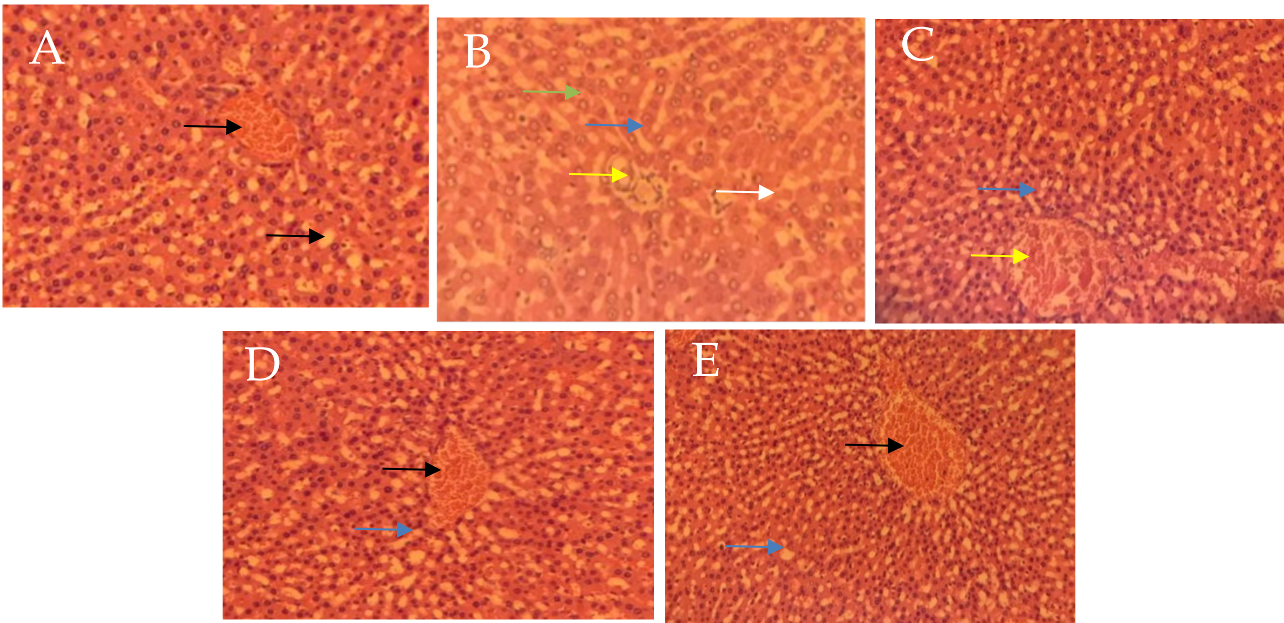


**Figure 3.** Histopathology of kidney tissue in doxorubicin-induced rats. Observations were made after staining using HE under a microscope. A: Group I showed normal glomerular and tubulus (black arrow), B: Group II, doxorubicin 67.75 mg/kg ($p<0.05$) showed glomerular necrosis (yellow arrow), tubulus have hyaline cast (white arrow), degeneration of tubulus (blue arrow), cell necrosis (green arrow), C: Group III, docorubicin 67.75 mg/kg + EELP 50 mg/kg (p<0,05), D: Group IV, docorubicin 67.75 mg/kg + EELP 100 mg/kg (p<0,05), E: Group V, docorubicin 67.75 mg/kg + EELP 200 mg/kg (p<0,05). Statistical analysis was carried out by SPSS 25 using one-way ANOVA, *post hoc tukey* test.

Histological examination of kidney organs was performed in each group. After 4 weeks of treatment, the animals were sacrificed and their kidneys were taken. Kidney organs were prepared into preparations for histology, based on the results of histological images, group II (doxorubicin) was the group with the most severe tissue damage. The score of damage to the nephrons due to doxorubicin-induced of 67.75 mg/kg can be seen in Table 2. There was no significant difference between the EELP groups and the control group ($p>0.05$). The control group had a score of damage (percentation) of 1.00±1.00, while the groups were given doxorubicin such as group II, III, IV, and V had damage rates of 88.00±6.25, 9.33±5.51, 10.67±4.16, and 7.00±4.00, respectively. The administration of doxorubicin proved that this drug can cause nephron damage, where there was a significant difference between the control group and group II ($p<0.05$).

**Table 2.** The score of damage to the nephrons due to doxorubicin-induced

| Group | % Damage of nephrons ± SD | The level of damage |
|---|---|---|
| I | 1.00±1.00[b] | 1 (≤10%) |
| II | 88.00±6.25[a] | 5 (>76%) |
| III | 9.33±5.51[b] | 1 (≤10%) |
| IV | 10.67±4.16[b] | 2 (11-25%) |
| V | 7.00±4.00[b] | 1 (≤10%) |

[a]Significant difference with control group (n=3, p< 0.05).
[b]Significant difference with group II (n=3, p< 0.05).

The damage that occurs such as, necrosis of the glomerulus and kidney cells, hyaline cast and tubular degeneration which clearly occurs due to doxorubicin administration. Cell degeneration is an event of cell morphological changes due to injury and can be both reversible and irreversible. These cell changes occur when cells do not able to maintain ionic and fluid homeostasis [37]. Hyaline cast to be a sign that the tubule will undergo necrosis. This sign appears as a result of cells experiencing hyperproteinemia [38]. When cells undergo necrosis, there will be changes in organ function accompanied by pain. Bowman's space widening due to atrophy glomerulus, which is a decrease in tissue size caused by a decrease in the number of cells or reduction in cell size [39]. This damage results in disruption of the blood filtration process. If the filtering ability of the blood is reduced, then blood cells and protein can be excreted with the urine or even accumulate in the tubules because they can pass through the filtration process [40].


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Administration of doxorubicin can cause an imbalance between the number of free radicals and natural antioxidants so that it has an impact on tissue damage through lipid peroxidation and protein oxidation [41]. The toxic effects of doxorubicin on renal cells were due iron dependent oxidative damage of biological macromolecules, membrane lipid peroxidation, and protein oxidation. The most frequent occurrences in the histological observations of doxorubicin-induced rat kidneys were decreased glomerular permeability and tubular atrophy [42, 43]. In this study, EELP proved to be able to increase the value of GSH and suppress the value of MDA which will provide a protective effect on the kidneys. In addition, it was reported that the flavonoid compounds contained in the test material were anti-inflammatory through their activity by inhibiting the cyclooxygenase (COX) enzyme. COX suppression will have an impact on reducing kidney damage [44, 45]. The histology results showed group V (Doxorubicin 67.75 mg/kg + EELP 200 mg/kg) has a good activity for nephroprotective compared to group IV and group III ($p<0,05$). Group V can be decreasing kidneys damage because of doxorubicin-induced showed with Glomerular change to be normal like in group I. Phenol and flavonoid compounds in the extract have an important function in life. The compounds can be external antioxidants that can help if the natural antioxidant are in a low state [46].

## 3. CONCLUSION

Doxorubicin can cause kidney damage with a low to severe level of damage. The damage is triggered by an increase in free radicals and a decrease in natural antioxidants. Therefore, natural ingredients such as *Lansium parasiticum* leaves can be used to protect the kidneys because they are antioxidants. EELP at a dose of 200 mg/kg has the best activity as a nephroprotective agent.

## 4. MATERIALS AND METHODS

### 4.1. Materials

All chemicals used in this study were obtained from authorized suppliers and specifically for analysis. To test the antioxidant activity, total phenol and total flavonoid are needed ethanol p.a, methanol p.a, folin ciocalteu reagent, gallic acid, sodium carbonate, sodium nitrate, aluminum chloride, sodium hydroxide, quersetin, 2,2-diphenyl-1-picrylhydrazyl (DPPH) and were obtained from Merck and Sigma Aldrich. Testing materials for urea and creatinine levels obtained from the health laboratory of North Sumatra, Medan, Indonesia. Serum biochemical study was done using chemicals reagent like malondialdehyde Elisa kit from Elabscience, phosphoric acid, n-butanol, and 5,5'-dithiobis-2-nitrobenzoic acid [DTNB] from Merck. This test was carried out in the laboratory of pharmacology, faculty of pharmacy, Universitas Sumatera Utara, Indonesia.

### 4.2. Extract preparation

*Lansium parasiticum* leaveas were collected from Delitua, Deli Serdang, North Sumatra, Indonesia. The samples were prepared for get simplex of sample. The extract was done to preparation by maceration method using ethanol solvent. Maceration lasted for 24 hours, and repeated 3 times. The filtrat from maceration process was collected and evoporated using rotary evaporator to get extract ethanol of *Lansium parasiticum* (EELP) [47].

### 4.3. Antioxidant activity, total phenolic and flavonoid content

Antioxidant activity in this study was determined using the DPPH method. The EELP solution in methanol was reacted with 5 mL of 0.5 mM DPPH. The solution was incubated in a lightly shaded place for 30 minutes and at room temperature. Measurements were carried out using a UV-Vis spectrophotometer at a wavelength of 517 nm. The absorbance used to determine the inhibitory concentration of 50 ($IC_{50}$) [48].

Determination of total phenol was carried out using the Folin-Ciocalteu method. In this experiment, gallic acid was used as the standard. The absorbance was obtained by measuring the test solution using a UV-Vis spectrophotometer at a wavelength of 765 nm [49]. While the total flavonoids were determined using the colorimetric method. The complex formed between the sample and 10% aluminum chloride solution was measured for absorbance using a UV-Vis spectrophotometer at a wavelength of 510 nm [50].


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### 4.4. Study design

This study used 30 male rats obtained from the Animal House, Faculty of Pharmacy, University of North Sumatra. Animals were divided into 5 test groups as below:

- Group I : As a control and were received normal saline
- Group II : Were received doxorubicin at a dose of 67.75 mg/kg/ 2 days before sacrifice i.v
- Group III : Were received EELP at a dose of 50 mg/kg/day for four weeks orally + doxorubicin at a dose of 67.75 mg/kg/ 2 days before sacrifice i.v
- Group IV : Were received EELP at a dose of 100 mg/kg/day for four weeks orally + doxorubicin at a dose of 67.75 mg/kg/ 2 days before sacrifice i.v
- Group V : Were received EELP at a dose of 200 mg/kg/day for four weeks orally + doxorubicin at a dose of 67.75 mg/kg/ 2 days before sacrifice i.v

After 4 weeks of treatment period, rats were anesthetized by ketamine at a dose of 70 mg/kg. Blood samples were collected for serum preparation. Kidneys were excised carefully after biopsy, washed with cold physiological saline and frozen for biochemical studies [51].

### 4.5. Determination of malondialdehyde (MDA)

Homogeneous solution of kidney tissue was added solution A (1 mL of 0.6 % 2-thiobarbituric acid, 3 mL of 1 % phosphoric acid, and 0.1 mL of distilled water). After 45 min boiling in water bath, the mixture was cooled, and then 4 mL of n-butanol was added to extract the cold thiobarbituric acid reactants. After that, 4 mL of n-butanol was added, and the samples were centrifuged at 3000 ×g for 5 min for separating butanol layer. n-butanol layer optical density was determined by spectrophotometry. A standard curve of MDA was created. MDA concentration was expressed as µg/mg protein [52].

### 4.6. Determination of glutathione (GSH) content

The sample solution was reacted with NTB. The reaction product was measured at a wavelength of 412 nm. The absorbance levels obtained were analyzed to obtain GSH in the test sample [52].

### 4.7. Determination of urea and creatinine value

The urea content of samples were determined by the glutamate dehydrogenase method. Serum was added with buffer solution and urease enzyme to hydrolyze urea in serum. Ammonia formed from hydrolysis will react with ketoglutarate and NADH and the enzyme glutamate dehydrogenase (GLDH). After 1-2 minutes the absorbance was measured at 700 nm wavelength (Absorbance 1), 2 minutes later the absorbance was measured again at a wavelength of 340 nm (Absorbance 2) [53].

The creatinine content of samples were determined by creatinine jaffe. The sample solution was alkalinized using NaOH, then reacted with picric acid to form a complex. After the reaction lasts 1-2 minutes measured absorption at a wavelength of 552 nm (Absorbance 1), 2 minutes later measured again absorption at a wavelength of 659 nm (Absorbance 2) [54].

### 4.8. Examination of kidney damage with histopathology

Kidney examination of experimental animals was carried out by observing the staining preparations under a microscope. Animal kidneys were taken and put into a buffer solution formalin. Then preparations were made and stained with hematoxylin and eosin [55]. Histopathological examination was carried out and based on work procedures applied in the anatomical pathology laboratory, Universitas Sumatera Utara, Indonesia. To measure the percentage of damage, it is done semi-quantitatively, read 100 parts of the tissue with a magnification of 400x in the area the outer border of the medulla with the inner cortex. Calculated amount damage and determined level of kidney damage based on the percentage of nephron damage is 0 (0%), 1 (≤10%), 2 (11%-25%), 3 (26%-45%), 4 (46%-75%) and 5 (>76%) [55].

### 4.9. Statistical analysis

All data on both antioxidant, total phenolic and flavonoid activity tests were the average of triplicate analyses. The data were recorded as mean ± standard error meaning (S.E.M.). Significant differences between means were determined using the student's t-test, p values and one-way ANOVA, *post hoc tukey* test.


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