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Nephrotoxicity effect of Ginseng Bugis (*Talinum paniculatum* (Jacq) Gaertn) leaves ethanolic extract on creatinine, urea, and kidney histopathological features

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Abstract

The prolonged use of traditional medicines in large doses is known to potentially cause organ failure, with the kidneys being particularly susceptible. Therefore, the present work aimed to determine the effect of *Talinum paniculatum* (Jacq.) Gaertn leaves ethanolic extract on serum creatinine and urea parameters, as well as kidney histopathological features, in an animal model. The rats used were separated into four groups. Group I (control) was given Na-CMC 1% (w/v); while groups II, III, and IV were administered ethanolic extract of Ginseng Bugis leaves at doses of 0.8, 1.6, and 2.4 g/kg bw, respectively. The extract was induced orally for 28 days, while the serum creatinine and urea levels were measured using human analyser on days 0 and 29. Additionally, a necropsy for organ retrieval of the kidneys was conducted on day 15. Tissue processing was then carried out for histopathological examination by Haematoxylin Eosin (HE) staining. Based on One way ANOVA statistical analysis on creatinine and urea levels, ethanolic extract of Ginseng Bugis leaves at doses of 0.8, 1.6, and 2.4 g/kg bw had no nephrotoxic effects. Regarding the histopathological features of the kidneys, the dose of 0.8 g/kg bw caused no abnormalities.

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Introduction

Indonesia is renowned as a rich source of raw materials for traditional medicines with potential healing properties for various diseases. The use of plants as medicine has been long practiced, but historical documentation on this subject is limited (Nugroho *et al*., 2022). One of the indigenous plants in Indonesia is *Talinum paniculatum* (Jacq.) Gaertn. This plant has roots similar to the *Panax* Ginseng plant, thus resulting in the name Ginseng. In South Sulawesi province of Indonesia, the plant is called Ginseng Bugis (Emelda *et al*., 2020). The root is known to possess a tonic effect, and believed to have benefits to the body system (Santoso *et al*., 2016; Sulistiono *et al*., 2017). Ginseng leaves contain protein, magnesium, potassium, ascorbic acid, phenonugrlic, flavonoids, and iron, which provide beneficial effects (Moura *et al*., 2020; Menezes *et al*., 2021). The use of medicinal herbs or traditional medicine is assumed to be safe, but potential toxicity might occur, either at a low or high dose, during long-term usage. Therefore, studies on toxicity of plants are needed to ensure proper use of medicinal plants (Bose *et al*., 2021).

Furthermore, inappropriate use of natural materials potentially damages the organs, with the kidneys being particularly susceptible. Therefore, testing the toxicity of a plant is essential for its therapeutic use (Sani *et al*., 2021). The kidneys, responsible for filtering approximately 25 - 30% of cardiac output, are particularly vulnerable to damage due to their role in processing blood containing toxic substances from the systemic circulation. Therefore, the kidneys are susceptible to significant pathological changes (Vázquez *et al*., 2022).

A common plant often used in medication is Ginseng Bugis. Previous studies reported that Ginseng Bugis leaves have immunomodulatory activity, along with anti-rheumatoid arthritis effect at doses of 0.8, 1.6, and 2.4 g/kg bw (Emelda *et al*., 2019).

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The safety assessment of medicinal plants is a crucial step during drug development. Determining the toxicity of medicinal plants is necessary for application in bioassay screening (Abubakar *et al*., 2020).

Serum creatinine and urea are the standard parameters to measure kidney function. Creatinine is a waste product of creatinine phosphate metabolism formed in the muscles, while urea is produced in the liver from amino acids (Astawibawa *et al*., 2022). Elevated levels of creatinine and urea show potential damage and a decline in kidney function. Kidney cell breakdown further impairs the filtration system, leading to increased creatinine and urea levels (Wolfensohn and Lloyd, 2013).

An alternative method to examine the kidney function is to observe the histological features. This method enables the observation of crystal damage, hydropic degeneration, oedema, fat degeneration, congestion, necrosis, inflammation, and haemorrhage. Changes in the histological features of the kidneys may result in an influx of numerous compounds into the body (Chinnappan *et al*., 2019). Therefore, the present work used nephrotoxicity testing to investigate the effects of ethanolic extract. The outcomes were evaluated using creatinine and urea parameters, as well as kidney histopathological changes in white rats.

Materials and methods

Equipment and materials

The tools used were rotavapor (rotary vacuum evaporator; IKA®), maceration vessels, animal scales (Ohaus®), digital scales (Ohaus®), centrifuges (PLC series), micropipettes (Huawei®), human analyser (Microlab 300), glass slides, and microtomes.

The materials used included distilled water, Ginseng Bugis leaves from South Sulawesi, 70% ethanol, Na-CMC (sodium carboxymethyl cellulose), urea and creatinine reagents, alcohol, xylol, Haematoxylin and Eosin staining (HE), paraffin, and formalin buffer.

Methods

Extraction

Ginseng Bugis leaf sample was macerated using ethanol 70%. The macerate was separated by filtration, then the solution was evaporated and lyophilised to obtain a dry extract (Emelda *et al*., 2017).

Suspension of ethanolic extract

Suspension of ethanolic extract was conducted by adding successive amounts of 2.4, 4.8, and 7.2 g. Subsequently, the samples were suspended into 30 mL of Na-CMC 1%.

Animal model

The animal model was *Rattus norvegicus* with characteristics of being male, healthy and clean, Wistar strain, 8 - 12 weeks old, and weighing 150 - 230 g. Before conducting the treatment, the rats were adapted to their environment within 2 w, followed by weighing and marking.

Assay

After the adaptation process, the rats were fasted for 16 – 18 h before the treatment. The blood samples were taken for the initial stage of creatinine and urea measurement. Furthermore, the rats were divided into four groups, each consisting of six members. Group I (control) was injected with 1% of Na-CMC, while groups II, III, and IV (tested groups) were injected with ethanolic extract of Ginseng Bugis at doses of 0.8, 1.6, and 2.4 g/kg bw, respectively. All the treatment steps were conducted once a day for 28 d through oral injection. Finally, blood collection as well as initial and final rate measurement of creatinine and urea were conducted on day 29 using a human analyser (Ethical clearance number: UMI011907271).

Production of kidney histology preparate

The histopathological examination was conducted through fixation of kidneys using a Formalin Neutral Buffer solution of 10%, followed by cutting and putting into a plastic specimen pan. Furthermore, the dehydration process was performed on three different concentrations of alcohol, namely 70, 80, and 90%. The next step was the purification process using xylol, followed by placement into paraffin, and storage in refrigerator. A microtome was used to cut paraffin blocks into thin slices in the range of 5 - 6 μm. Finally, the slices were floated in warm water (60°C) to hinder multiplying tissues for 24 h. Afterward, the slices were lifted, placed into a glass slide for Haematoxylin and Eosin (HE) staining, and observed under a microscope (Abebe *et al*., 2021; Lazuardi *et al*., 2022; Yuniarti *et al*., 2023).

Statistical analysis

The creatinine and urea data were processed statistically using One-way ANOVA. The results of the One-way ANOVA was performed on all treatment groups for creatinine and urea levels with obtained values of $p = 0.207$ and $p = 0.359$, respectively. This indicated that both the values were > 0.05, which meant that there was no statistically significant difference between each treatment group. Since there were no significant differences, no advanced statistical analysis was performed.

Results and discussion

The present work used various extract doses of 0.8, 1.6, and 2.4 g/kg bw on male Wistar rats. The selection of dose variations was based on a previous study in which extract doses of 0.8, 1.6, and 2.4 g/kg bw provided immunomodulatory and anti-inflammatory activities (Emelda *et al*., 2019). Therefore, the present work aimed to determine the nephrotoxic effect of these doses.

The experimental animals used were male rats of the Wistar strain, commonly used in studies due to their wide availability. Based on previous reports, male rats have a more stable hormonal system than females. The present work preferred male rats over females in the experiment due to concerns about female hormone cycles causing behavioural variations that could skew the results (Lovick *et al*., 2021; Mohd Azam *et al*., 2022). The effect of the extract on serum creatinine and urea levels in all treatment groups is shown in Tables 1 and 2.

Table 1 shows the measurement results for initial creatinine levels before treatment. Group I (control) produced a creatinine value of 0.658 ± 0.074 mg/dl, while groups II, III, and IV yielded 0.653 ± 0.080, 0.585 ± 0.077, and 0.618 ± 0.069 mg/dl, respectively. These results signified that initial creatinine levels for all groups were within the normal range of 0.2 - 0.8 mg/dl. The final creatinine level in group I (control) was 0.621 ± 0.064 mg/dl, while groups II, III, and IV obtained values of 0.606 ± 0.109, 0.660 ± 0.103, and 0.636 ± 0.086 mg/dl, respectively. Based on the results, the final creatinine level decreased in the control and the 0.8 g/kg bw extract group. An increase was observed in the extract group at a dose of 1.6 and 2.4 g/kg bw, but within normal values.

Table 2 shows the measurement results of initial urea levels before treatment. Group I (control) produced a urea value of 19.30 ± 1.55 mg/dl, while groups II, III, and IV obtained values of 19.81 ± 1.74, 19.51 ± 1.94, and 19.43 ± 1.83 mg/dl, respectively. These results signified that the initial urea levels for all groups were within the normal range (8 - 23 mg/dl). The final urea levels in group I (control) was 19.43 ± 1.83 mg/dl, while groups II, III, and IV yielded values of 19.90 ± 1.87, 19.81 ± 1.88, and 20.0 ± 1.16 mg/dl, respectively. These results showed that the final urea level had increased but within the normal range.

Table 1. Creatinine levels and their increments in all treatment groups.

Treatment group	Average level of creatinine (mg/dL)		% Increment
	Initial ± SD	Final ± SD	
(I) Control	0.658 ± 0.074	0.621 ± 0.064	-5.958%
(II) Extract 0.8 g/kg bw	0.653 ± 0.080	0.606 ± 0.109	-7.755%
(III) Extract 1.6 g/kg bw	0.585 ± 0.077	0.660 ± 0.103	12.878%
(IV) Extract 2.4 g/kg bw	0.618 ± 0.069	0.636 ± 0.086	2.830%

Table 2. Urea levels and their increments in all treatment groups.

Treatment group	Average level of urea (mg/dL)		% Increment
	Initial ± SD	Final ± SD	
(I) Control	19.30 ± 1.55	19.43 ± 1.83	0.66%
(II) Extract 0.8 g/kg bw	19.81 ± 1.74	19.90 ± 1.87	0.45%
(III) Extract 1.6 g/kg bw	19.51 ± 1.94	19.81 ± 1.88	1.51%
(IV) Extract 2.4 g/kg bw	19.43 ± 1.83	20.0 ± 1.16	2.85%

Based on the final serum creatinine and urea levels, it was concluded that the rats did not experience kidney damage. This is based on references stating that elevated concentrations of urea and creatinine in the serum show a decrease in kidney function. An increase in blood urea concentration is associated with a decrease in kidney function, resulting in decreased glomerular filtration rate and impaired excretion (Emeribe *et al*., 2021).

The results of creatinine and urea levels were statistically processed using One way ANOVA. Both levels had $p > 0.05$, implying no significant differences among the treatment groups.

Figure 1 shows the histopathological examination results of the kidneys obtained using a microscope. Based on the results, there were no abnormalities in the histological appearance in the control and the extract group of 0.8 g/kg bw dose. However, abnormalities such as hydropic degeneration and inflammation were observed in the extract groups of 1.6 and 2.4 g/kg bw.

Hydropic degeneration is characterised by inflammation of the cytoplasm resulting from an accumulation of excess fluid due to a failure in maintaining homeostasis and fluid regulation in cells. This condition manifests as cell swelling, empty spaces (vacuoles), and enlarged and condensed cells. Furthermore, hydropic degeneration is a reversible cell injury with intracellular accumulation that is more severe in the presence of albumin. The aetiology is similar to cell swelling, but the intensity of pathological stimuli is more severe and the exposure time is longer, as commonly observed in epithelial cells.

Inflammatory processes are natural immune reactions crucial for the defence system of the body against various hazards. This process also improves the structure and function of the tissue caused by the hazard.

The nephrotoxic effect assessment for Ginseng Bugis leaf extract at doses of 0.8, 1.6, and 2.4 g/kg bw showed that the treatment was safe for test animals up to 28 d based on the creatinine and urea parameters. Further observations were carried out on the histopathological features of the kidneys. Observations in the control group and at a dose of 0.8 g/kg bw did not show any abnormalities. At doses of 1.6 and 2.4 g/kg bw, hydropic degeneration and inflammation were observed as a natural body defence system response to disturbances.

In previous studies, extract doses of 0.05, 0.1, and 0.15 g/kg bw showed immunomodulatory and anti-rheumatoid activities. Additionally, the extract has shown aphrodisiac effects on the libido of Wistar male rats at a dose of 55 mg given orally (Emelda *et al*., 2020; Septiani *et al*., 2021). Based on the results, extract doses below 0.8 g/kg bw did not exert a nephrotoxic effect.

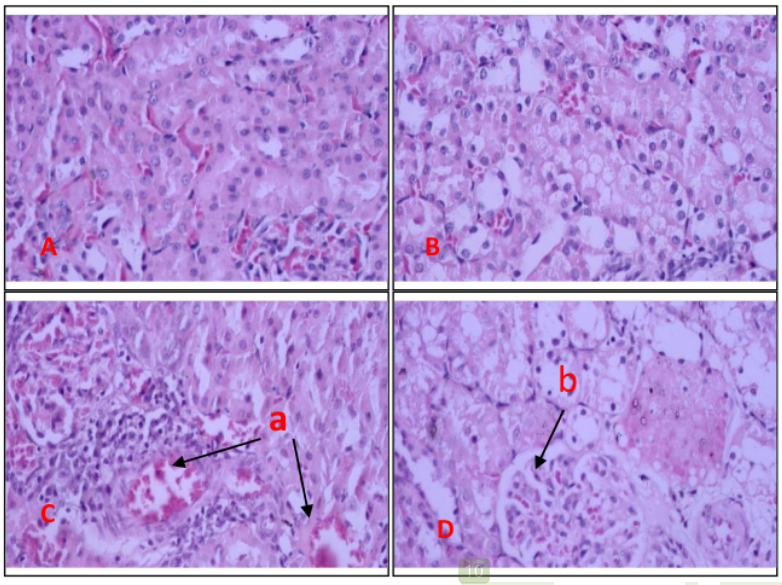

Figure 1. Kidney histology. A: control group; B: extract at 0.8 g/kg bw; C: extract at 1.6 g/kg bw; D: extract at 2.4 g/kg bw; a: inflammation; and b: hydropic degeneration.

Conclusion

The administration of Ginseng Bugis leaves (*Talinum paniculatum* (Jacq.) Gaertn) ethanolic extract at doses of 0.8, 1.6, and 2.4 g/kg bw for 28 days in white rats (*Rattus norvegicus*) had no nephrotoxic effect based on creatinine and urea parameters. In addition, the 0.8 g/kg bw dose caused no abnormalities in the renal histology.

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