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The Effectiveness of Cinnamon Extract (*Cinnamomum burmannii*) to Reducing Ureum Level in Male *Rattus norvegicus* Unilateral Ureteral Obstruction (UUO) Model

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Abstract

Cinnamon extract's effectiveness as a renoprotective has not been previously investigated due to its widespread use in daily life, either as a cooking ingredient or as a herb. The aim of this study is to determine the effectiveness extract of cinnamon (Cinnamomum burmannii) as a renoprotective in lowering urea levels in the kidneys. An in vivo experimental study with a pre-post test and control group design was conducted at the Faculty of Medicine's Animal House and Biotechnology Laboratories. Male white rats (Rattus norvegicus) were used as the research subjects. Thirty rat were divided into five groups: negative control, positive control, cinnamon extract at 50 mg/kgBW, 100 mg/kgBW, and 200 mg/kgBW. The data were processed using SPSS 22.0. Cinnamon extract doses of 100 mg/kgBW and 200 mg/kgBW were the most effective in reducing urea levels and suspending the progression of the renal fibrosis process in Wistar male white rats with unilateral ureteral obstruction (UUO) model.

Keywords: Cinnamon, In vivo, Unilateral ureteral obstruction (UUO), Ureum

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1. Introduction

The kidney is a vital organ of the body since it functions to eliminate metabolic waste, either in its active form or as a metabolite. Treatment costs for patients with chronic kidney disease tend to be expensive with poor outcomes.[1,2] It is estimated that almost 10% of the world's population has chronic kidney disease. Meanwhile, in Indonesia, the Indonesian Society of Nephrology (InaSN) reports a growth approaching the exponential rate in end-stage kidney disease.[3,4]

If the kidneys are injured, urea and creatinine levels will increase. The value of urea is one of the parameters that can be evaluated.[5] Urea is produced in the kidneys as a byproduct of catabolism. The normal value of urea in rats is 12.3-29.6 mg/dL. [6,7] An increase in the value of urea can be caused by an inflammatory process or kidney tissue injury, which will lead to inflammation.[5,7–9] Whether this process is repeated continually,

the kidneys become incapable of performing their tasks in the body, a condition known as kidney fibrosis. Kidney fibrosis is a pathological repair reaction caused by pathogenic causes such as inflammation and cell injury in the kidney. Kidney fibrosis can also develop due to an abnormal accumulation of extracellular matrix proteins caused by an imbalance in the matrix's production and degradation. Generally, fibroblasts in kidney tissue play a critical role in the progression of kidney fibrosis. Fibroblasts become activated when the kidneys sustain injury and synthesize an extracellular matrix composed of collagen-1, collagen-2, hyaluronic acid, laminin, hydroxyproline, and α-SMA.[10,11]

Once fibroblasts are stimulated, their production of proinflammatory cytokines such as interleukin 6 (IL-6) and tumor necrosis factor (TNF-) is significantly increased. Additionally, these cytokines have a significant role in the development of fibrosis. According to Rolando et al. 2021, kidney fibrosis can be prevented with effective treatment, specifically treatment derived from herbal ingredients, one of which is ingredients containing alkaloids, cinnamaldehyde, flavonoids, polyphenols, and saponins, such as mangosteen peel extract, avocado leaf extract, or cinnamon extract.[12]

Budi S et al. demonstrated in 2016 that African leaves (Vernonia amygdalina) were capable of lowering urea levels in white male rats (Rattus novergicus) kidney failure model rats due to their flavonoids and saponins composition.[13] According to Muhyi YD et al., mangosteen rind extract (Garcinia mangostana L.) was also capable of lowering urea levels in white male rats (Rattus norvegicus) induced by Isoniazid due to the presence of chemical substances, specifically flavonoids. [14] Alkaloids, flavonoids, saponins, and tannins can effectively lessen the formation of lipid peroxides by scavenging free radicals and raising intracellular antioxidant concentrations. Cinnamon extract is considered to have the ability to decrease urea levels in white male rats (Rattus norvegicus) using the Unilateral Ureteral Obstruction (UUO) model.[15,16]

Cinnamon is one of the spices widely used as a flavor element in cuisine. Cinnamon (Cinnamomum burmannii) is a plant originating from Sumatra. Indonesia produces 90,000 tons of cinnamon annually.[17,18] Cinnamon's application in daily life, whether as a cooking component or as a herbal remedy, is not commonly understood, particularly in terms of cinnamon extract's renoprotective properties. Thus, additional research is required to discover whether cinnamon extract (Cinnamomum burmannii) is able to take action as a renoprotector by lowering the value of urea in the kidneys.

2. Method

This type of research is a true experimental laboratory in vivo using a pre-test post-test with a controlled group designed to determine the effectiveness of reducing urea levels in male white rats (Rattus norvegicus) with a unilateral ureteral obstruction (UUO) model. The research was conducted at the Animal House Laboratory and the Biotechnology Laboratory, Faculty of Medicine,

Sriwijaya University. The sample of this study was a male white rat (Rattus norvegicus) wistar strain that had been previously intervened as a unilateral ureteral obstruction (UUO) model. This research has been approved by the Faculty of Medicine, Sriwijaya University's research ethics and health ethics commission (KEPKK) under certificate number 009-2022.

Cinnamomum burmannii extract

Cinnamon powder extract was macerated for three days at room temperature in a chocolate bottle with 96 percent ethanol solvent. The bath is then filtered, the filtrate is collected, and the residue is re-immersed in the same solvent. This procedure was carried out five times. To obtain a thick extract, the filtrate was collected and the solvent was evaporated using a rotating vacuum evaporator (at a temperature of 50°C). Subsequently, the viscous extract was extracted with the aid of a freeze-dryer to yield a dry extract. The dry extract obtained was weighed to determine the yield produced.

Animal subject

There were five treatment groups in this study: cinnamon extract at 50 mg/kgBW, 100 mg/kgBW, 200 mgkgBW, distilled water as a negative control, and methylprednisolone as a positive control. Wistar rats will undergo a seven-day UUO treatment to induce kidney fibrosis. Five groups of male white rats (Rattus norvegicus) were formed.The first group received methylprednisolone 40mg/kgBW for fourteen days as a positive control. The second group was given 1cc of distilled water for fourteen days as a negative control. Cinnamon extract 50mg/kgBW was given to the third group for 14 days. For fourteen days, the fourth group received cinnamon extract containing 100mg/kgBW. Cinnamon extract was administered to the fifth group at a dose of 200mg/kgBW for 14 days.

Urea analysis

Urea levels were determined on the first day prior to the rats being treated to renal fibrosis with UUO, on the seventh day following fibrosis, and finally on the 21st day following 14 days of cinnamon extract intervention. Blood was collected from the eye veins of rats' retro-orbital plexus using 5ml of microhematocrit, and then urea was determined by spectrophotometry.

Once the blood has been left to stand for 15 minutes, it is centrifuged for 10 minutes at 3000 rpm to extract the serum (the clear part of the blood) and other components. It is necessary to fill a test-tube halfway with serum, then mix it with 1 mL of working reagent, which is made up of four parts reagent one and one part of reagent 2, before homogenizing the mixture. A UV spectrophotometer (MicroLab 200) was used to measure the urea levels in the serum. The wavelength used was 505 nm, and the results were obtained using this method.

3. Result

The Saphiro-Wilk test demonstrated that the probability of urea levels was more than 0.05 in all groups, indicating that the data distribution was normal in all groups. Meanwhile, the urea levels were homogeneous from the homogeneity test, namely the Lavene Test. The data is said to be homogeneous if the value of p>0.05 is p = 0.050.

The Effectiveness of Cinnamon Extract Against Urea Levels

To determine the effectiveness of cinnamon extract on urea levels, paired t test (Paired-Sample T Test) was used and the results showed that negative control (aquades), positive control (methylprednisolon) and cinnamon extract at a dose of 50 mg/kgBW were not effective in reducing urea levels (p=0,507; 0,063 and 0,890), while cinnamon extract dose 100 and cinnamon extract dose 200 were effective in reducing urea levels significantly (p=0.000).

Table 1. The Effectiveness of Cinnamon Extract

Against Urea Levels

Group	Urea Level		Difference	p*
	Day 7	Day 21		
Control (-)	58,07 ± 0,75	57,24 ± 2,83	0,82 ± 2,19	0,507
Control (+)	58,07 ± 0,75	55,30 ± 1,17	2,77 ± 1,91	0,063
Cinnamon 50	58,07 ± 0,75	58,00 ± 1,08	0,06 ± 0,89	0,890
Cinnamon 100	58,07 ± 0,75	44,94 ± 1,36	13,12 ± 0,90	0,000
Cinnamon 200	58,07 ± 0,75	36,13 ± 0,53	21,94 ± 1,08	0,000

**Paired-Sample T Test, p = 0,05*

Comparison of the Effectiveness of Cinnamon Extract with Positive and Negative Controls on Reducing Urea Levels

Table 2. Comparison of the Effectiveness of Cinnamon Extract with Positive and Negative Controls on Reducing Urea Levels

Group	Mean ± SD	Group	Mean ± SD	**p*
Control (-)	57.24 ± 2.83	Control (+)	55,30 ± 1,18	0,273
		Cinnam 50	58,00 ± 1,08	0,644
		Cinnam100	44,94 ± 1,34	0,001
		Cinnam200	36,13 ± 0,53	0,000
Control (+)	55,30 ± 1,18	Cinnam 50	58,00 ± 1,08	0,015
		Cinnam100	44,94 ± 1,34	0,000
		Cinnam200	36,13 ± 0,53	0,000
Cinnamon 50	58,00 ± 1,08	Cinnam100	44,94 ± 1,34	0,000
		Cinnam200	36,13 ± 0,53	0,000
Cinnamon100	44,94 ± 1,34	Cinnam200	36,13 ± 0,53	0,000

**Independent T Test, p = 0.05*

The Shapiro-Wilk normality test indicates that the probability value for each group is more than 0.05, indicating that the data distribution for each group is normal; thus, the Independent T-Test was performed to compare the effectiveness of the urea levels in each group. The analysis's results are summarized in Table 2. Cinnamon extract doses of 100 mg/kgBW and 200 mg/kgBW were the most effective in reducing urea levels in white male rats with UUO.

Dosage Conformity Between Cinnamon Extract and Methylprednisolone Against Reducing Ureum Levels

A probability value of 0.050 (p = 0.05) indicates that the levels of all groups are homogeneous, and hence the post hoc confirmation test using the LSD test generates the following results:

Table 3. Dosage Conformity Between Cinnamon Extract and Methylprednisolone Against Reducing Ureum Levels

	Negative	Positive	Cinna50	Cinna100	Cinna200
Negative		0,449	0,985	0,000	0,000
Positive	0,449		0,130	0,000	0,000
Cinna50	0,985	0,130		0,000	0,000
Cinna100	0,000	0,000	0,000		0,000
Cinna200	0,000	0,000	0,000	0,000	

**LSD test p=0.05*

The LSD test revealed no difference in efficacy between cinnamon extract at a dose of 50mg/kgBW and positive control for reducing urea levels. Furthermore, there were differences in the effectiveness of urea levels at 100mg/kgBW and 200mg/kgBW cinnamon extract doses. Therefore, 100 mg/kgBW and 200 mg/kgBW are the most effective doses for reducing urea levels in Wistar male white rats with UUO.

4. Discussion

Cinnamon extract at doses of 100 mg/kgBW and 200 mg/kgBW effectively lowered urea levels in Wistar rats with the UUO model. Meanwhile, administration of cinnamon extract at a dose of 50 mg/kgBW decreased urea levels slightly. 100 mg/kgBW and 200 mg/kgBW doses were more effective at lowering urea levels than 50 mg/kgBW doses. The rats given cinnamon extract at doses of 100 mg/kgBW and 200 mg/kgBW had the lowest urea levels.

Serum urea can represent not only kidney injury but also the typical response of the kidneys to depleted extracellular volume or decreased renal blood flow, allowing urea to be used as a measure to assess kidney function. Elevated urea levels indicate impaired renal function. Damage to the kidneys (Unilateral Ureteral Obstruction) causes a decrease in kidney function.

Unilateral Ureteral Obstruction (UUO) is a model of acute kidney injury leading to the development of renal tubulointerstitial fibrosis developed by Ucero (2014) and is currently being utilized as a model for research into acute kidney injury and renal fibrosis. The events that occur after 3 hours of UUO begin with a decrease in renal blood flow and glomerular filtration rate (GFR), which is followed by hydronephrosis, macrophage infiltration, and tubular epithelial cell death, which can be characterized by an increase in urea and creatinine level.[19]

Kidneys that are damaged are unable to filter incoming urea, resulting in elevated urea levels in the circulation. This condition impairs the body's metabolic, fluid, and electrolyte balance, resulting in uremia, or the retention of urea and other nitrogenous wastes in the blood.[5,8,20] Kidney damage compensates for itself through a repair reaction. A pathological repair reaction can occur in the kidney.

Urea will build up in the blood if the kidneys are injured. Plasma urea elevation shows that the kidneys are not performing their filtering role properly. Uremia is a term that refers to a form of kidney failure that is defined by excessively high plasma urea levels. This illness is potentially fatal and may require dialysis or kidney transplantation.

Increased urea levels in the blood may be caused by an inflammatory process or by injury to the kidney tissue, which causes inflammation.[5,6]It makes no difference how many times this process is repeated because the kidneys eventually lose their ability to perform their functions in the body, resulting in a condition called kidney fibrosis. Furthermore, kidney fibrosis emerges as a result of an imbalance in the creation and breakdown of extracellular matrix proteins and also renal excretion products such as urea. Preventing kidney fibrosis can be accomplished through the use of effective treatments, specifically, treatments derived from herbal ingredients, one of which is ingredients containing cinnamaldehyde, alkaloids, , flavonoids, polyphenols, and saponins such as cinnamon extract.

Cinnamon extract is rich in alkaloids, flavonoids, polyphenols, saponins, safrole, tannins, cinnamaldehyde, and triterponoids, all of which have anti-oxidant and anti-inflammatory properties. Cinamaldehyde is another major active component of cinnamon extract that has been shown to inhibit the activity of urea. Additionally, the active compound polyphenol from cinnamon in the form of cinnameldehid which acts as an antioxidant can reduce urea levels. The mechanism that plays a role is by suppressing oxidative stress from various oxidative reactions that occur in the kidneys. These chemical compounds such as alkaloids, flavonoids, cinnamaldehyde, tannins, polyphenols and saponins can inhibit the occurrence of lipid peroxides by preventing free radicals and increasing the concentration of intracellular antioxidants.[15,21,22]

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free radicals and increasing the concentration of intracellular antioxidants.[18,23]

Cinnamon's active constituents, such as alkaloids, may also be beneficial in lowering urea levels in patients with kidney fibrosis. Alkaloids inhibit TGF- and α-SMA expression. Alpha-smooth muscle actin (α-SMA) is a marker that activates fibroblasts, which contributes to the fibrosis of an organ. Alkaloids also decrease fibroblast activity, hence reducing the fibrosis process in the kidneys. Reduced fibrosis in the kidneys improves kidney function, preventing urea from building up in the plasma and allowing it to be processed by the kidneys via the urea cycle. As a result, alkaloids and triterpenoids are effective in decreasing urea levels by suppressing TGF- and -SMA expression in the kidneys.[5,9]

Cinnamon extract doses of 100 mg/kgBW and 200mg/kgBW were effective doses for reducing urea levels in rats with previous UUO intervention. It is stated that the cinnamon extract follows a linear dose dependent pharmacokinetic characteristic; when the dose of cinnamon extract is increased twice, the plasma level also increases twice or proportionally; therefore, increasing the dose will produce the expected effect.

There are no comparable studies on the effect of urea reduction in patients with renal fibrosis to compare in this investigation. Thus, additional research is required to ascertain cinnamon's pharmacological effect on urea reduction in patients with renal fibrosis.

5. Conclusion

Cinnamon extract doses of 100 mg/kgBW and 200 mg/kgBW were shown to be the most effective for reducing urea levels and preventing the advancement of kidney fibrosis in Wistar male rats with unilateral ureteral obstruction (UUO).

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