

Efficacy of cinnamon (*Cinnamomum burmannii*) extract to decrease serum creatinine in acute kidney injury induced male wistar rats

Evi Lusiana¹, Nia Savitri Tamzil¹, Desi Oktarina²

¹Department of Pharmacology, Faculty of Medicine, University of Sriwijaya

²Department of Clinical Pathology, Faculty of Medicine, University of Sriwijaya

#Corresponding Author: mrs.evilusiana@gmail.com

Received : August 19th 2019

Accepted : October 28th 2019

ABSTRACT

Background

Kidney vital function as a regulator of blood volume and chemical composition to excrete solute and water selectively. Acute kidney injury (AKI) is a sudden decline in kidney function which is temporary, is marked by an increase in serum creatinine levels and decreased urine output.

Objective

This study aims to determine the effectiveness of cinnamon extract in acute kidney injury induced male wistar rats.

Method

An experimental *in vivo* with *pre-post control group design* was conducted in twenty-five wistar strain white rats that were divided into 5 treatment groups that received methylprednisolone as a positive control, aquades, and different dose of cinnamon extracts (50 mg/kgBW, 100 mg/kgBW, and 200 mg/kgBW). The rat model of acute kidney injury was prepared by the method of *unilateral ureteral obstruction* (UUO).

The effectiveness of cinnamon extract was carried out by creatinine levels checked using ELISA and analyzed by ANOVA.

Results

The extract of cinnamon can lower serum creatinine levels were significantly ($p < 0.05$). A dose of 100mg / KgBW is an effective dose in AKI compare to methylprednisolone.

Conclusion

Extract of cinnamon (*Cinnamomum burmannii*) corrected creatinine levels of acute kidney injury induced male wistar rats.

Keywords: Acute kidney injury, cinnamon extract, creatinine

Introduction

Kidney is an important organ in the body and serves to remove metabolic waste and toxins in the form of urine.¹ Acute kidney injury (AKI) results in the abrupt loss of kidney function, leading to the retention of waste products, electrolyte disturbances, and volume status changes. It is associated with significant increases in both short- and long-term morbidity and mortality.^{2,3,4}

Acute renal impairment or Acute Kidney Injury (AKI) can be defined as the rapid decline and sudden or severe kidney filtration function. This condition is usually characterized by an increase in serum creatinine concentration or azotemia (elevated BUN concentration). But usually soon after kidney injury occurs, the concentration levels of BUN back to normal.²

Acute kidney injury (AKI), previously known as acute renal failure (ARF) or acute renal failure (ARF) is a syndrome in the Nephrology field in the last 15 years showed an increased incidence. The incidence in developing countries, ordinarily in the community, difficult to obtain because not all AKI patients come to the hospital. It is estimated that the real incidence in communities far exceeds the figure recorded. Increased incidence of AKI among others associated with increased sensitivity of diagnostic criteria that cause milder cases can be diagnosed. Some reports in the world show the incidence varies between 0.5 to 0.9% in the community, from 0.7 to 18% in patients who are hospitalized, up to 20% in patients treated in the intensive care unit (ICU), with a mortality rate that was reported from around the world ranging from 25% to 80%.^{3,4}

Various studies have been conducted to determine the factors that underlie the occurrence of acute kidney injury to prevent or restore kidney function. Then came the models like the model of ischemia/reperfusion, immune injury, nephrotoxin and unilateral ureteral obstruction (UUO) which causes tubular damage, and interstitial renal glomerulus. Unilateral ureteral obstruction (UUO) was originally performed on dogs and rabbits, but now most of UUO performed on rats and rat. Unilateral treatment resulted in UUO kidneys cannot change the overall study, but have the advantage in lower mortality and the ability to control internal.⁵

Nowadays herbs developed to treat various diseases. *Cinnamomum burmannii* species is one of the herbs that are found in Indonesia. According to Rismunandar and Paimin (2003) cinnamon has various contents beneficial to health also proved to be anti-inflammatory, anti-fungal, antioxidant.^{6,7} According to the study of Chan et al, 2014 cinnamon extract contains flavonoids and polyphenols as an antioxidant and anti-inflammatory that can be used to improve the body's cells and treat a variety of conditions.^{8,9} Based on this, we need to study assessing the effects of extracts of cinnamon (*Cinnamomum burmannii*) against acute kidney injury (AKI) in the rat wistar.^{10,11,12}

Methods

This was experimental in vivo study with pre-post control group design. As many as twenty-five white male wistar rats were divided into 5 groups. The first group was administered with methylprednisolone as a positive control, the second group was administered with distilled water as a negative control, the third, fourth, and fifth group were administered with various doses of cinnamon extract items, namely 50 mg/KgBW, 100 mg/KgBW and 200mg KgBW.

Preparation cinnamon extract (*C.burmannii*)

Preparation of Powdered cinnamon extract macerated with 96% ethanol for 3 days at room temperature in a brown bottle. Then marinade filtered, the filtrate was stored while the residue was soaked in the same solvent. This treatment was repeated five times. The filtrate obtained was collected and then evaporated the solvent with a vacuum rotary evaporator (at 50 ° C) to obtain a thick extract. Subsequently, extract viscous dewatered using freeze-dryer to obtain a dry extract. The dry extract obtained, weighed to determine the yield generated.

Unilateral ureteral obstruction for acute kidney injury

Rat are anesthetized with Biophentyl 0,1cc / ml / kg by intraperitoneal injection. Shaved fur on flank regio (lateral part of the back). An incision with a scalpel, then obtained A.renalis then ligation in A. renalis. The wound was closed by stitching and daily wound care is done. Wait for 7 days post-surgery

Measurement of serum creatinine levels

Blood rat was taken by cutting a part of the neck veins that are housed in a test tube. Blood allowed to stand for 15 minutes, then centrifuged for 10 min at 3000 rpm to obtain serum (the clear part) of blood. Serum pipette of 0.5 mL fill in a test tube and then mixed with 1 mL of working reagent is a mixture of 4 parts of reagent 1 and 1 part of reagent 2, and then homogenized. Measurements were made using a UV spectrophotometer (MicroLab 200) at a wavelength of 505 nm, so that got creatinine levels serum.15

Results

All treatment groups were examined levels of creatinine on day 0 (before induction UUO), 7th (after induction UUO, before intervention with therapeutic cinnamon extracts and

methylprednisolone) and 21 (after induction UUO and has been in therapy with cinnamon extract or methylprednisolone).

Creatinine levels

To see the effectiveness of unilateral ureteral obstruction (UUO) on levels of creatinine then was examined for both parameters at day 0 before treatment and 7 after treatment UUO. From the paired-sample T-test and Wilcoxon showed there are differences in creatinine levels before and after treatment unilateral ureteral obstruction (UUO) where there is a significant increase in creatinine levels after treatment unilateral ureteral obstruction (UUO).

Table 1. The effectiveness of unilateral ureteral obstruction (UUO) on levels of creatinine

Treatment Group	Day 0 (Before treatment)	Day 7 (After treatment)	P
Negative control	20.69 ± 0.54	57.22 ± 1.62	0,000 *
Positive control	20.24 ± 0.38	58.48 ± 1.36	0.028 **
Cinnamon Extract 50	19.92 ± 0.64	57.32 ± 1.52	0,000 *
Cinnamon Extract 100	20.41 ± 0.49	58.68 ± 0.81	0,000 *
Cinnamon Extract 200	20.81 ± 0.61	58.13 ± 0.84	0,000 *

* Paired-Sample T Test, P = 0:05 , ** Wilcoxon test, p = 0:05

To see the effectiveness of cinnamon extract on creatinine levels were measured levels of creatinine each group the 7th day (after treatment UUO but has not interfered with the administration of cinnamon extract) and day 21 (after treatment UUO and have interfered with the administration of cinnamon extract), with the Shapiro-Wilk normality test obtained probability value of all groups of > 0.05, which means that each group of data distribution is normal except in the group, because the data were normally distributed then to look at the effectiveness of cinnamon extract on creatinine levels used paired t-test (paired-sample T-Test).

Table 2. The effectiveness of cinnamon extract on creatinine levels

Treatment group	Creatinine levels Day 7	Creatinine levels Day 21	Difference	P
Negative control	57.22 ± 1.62	58.55 ± 1.51	1.33 ± 0.44	0,001
Positive control	58.48 ± 1.36	60.69 ± 1.41	2.22 ± 2.20	0.057
Cinnamon Extract 50	57.32 ± 1.52	50.87 ± 1.39	6.45 ± 2.55	0,002
Cinnamon Extract 100	58.68 ± 0.81	37.53 ± 1.91	21.11 ± 1.92	0,000
Cinnamon Extract 200	58.13 ± 0.84	41.08 ± 1.68	17.47 ± 1.65	0,000

* Paired-Sample T Test, P = 0:05 , ** Wilcoxon test, p = 0:05

Table 2 shows the mean serum creatinine level of each group on days 7 and 21, Creatinine levels in each group day 7 and 21 then analyzed by paired t-test (paired-sample T-test) and Wilcoxon, the positive group obtained probability value > 0.05. This shows that there are differences between the mean serum creatinine level in the positive group. In addition, the probability value obtained negative group and all the extra dose of cinnamon <0.05, it indicates that there are differences between the mean serum creatinine level in the negative group and all doses of cinnamon extract where an increase in creatinine levels significantly in the negative group and the treatment group methylprednisolone, and there is a significant decrease in creatinine levels in all groups cinnamon extract all doses.

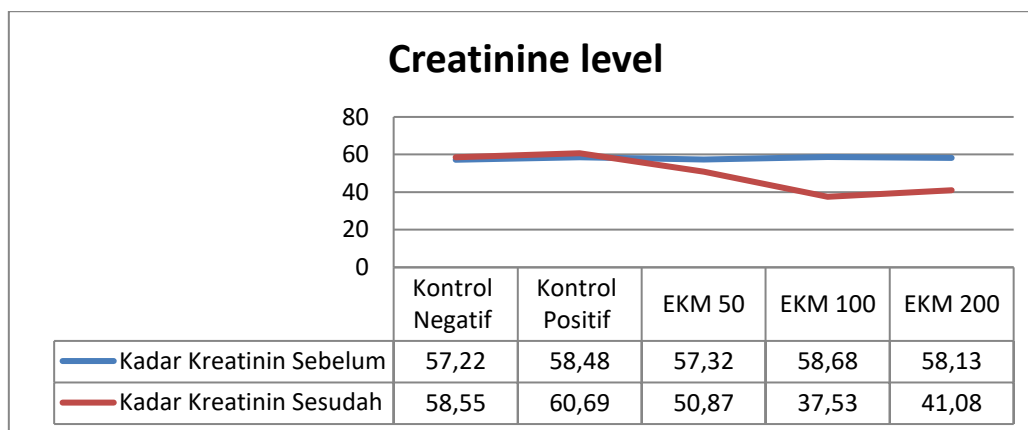


Figure 1. Effectiveness of cinnamon extract on creatinine levels

Creatinine levels day 21 all groups measured and tabulated. Furthermore, creatinine day 21 compared to each group. From the test results obtained Independent T-test probability value among all groups <0.05 so that it can be stated that there are differences between the

mean serum creatinine level day 21 among all groups. Cinnamon extract 100mg / kg dose was the most effective to reduce levels of creatinine strain Wistar male rats with UUO treatment.

Table 3. Comparison of the Effectiveness of Cinnamon Extract Creatinine Levels After Intervention (Day 21)

Group	The mean ± SD	Group	The mean ± SD	p value
Negative group	58.55 ± 1.51	Positive control	60.69 ± 1.41	0,029
		Cinnamon Extract 50	50.87 ± 1.39	0,000
		Cinnamon Extract 100	37.53 ± 1.91	0,000
		Cinnamon Extract 200	41.08 ± 1.68	0,000
Positive group	60.69 ± 1.41	Cinnamon Extract 50	50.87 ± 1.39	0,000
		Cinnamon Extract 100	37.53 ± 1.91	0,000
		Cinnamon Extract 200	41.08 ± 1.68	0,000
Cinnamon Extract 50	50.87 ± 1.39	Cinnamon Extract 100	37.53 ± 1.91	0,000
		Cinnamon Extract 200	41.08 ± 1.68	0,000
Cinnamon Extract 100	37.53 ± 1.91	Cinnamon Extract 200	41.08 ± 1.68	0.007

* *Independent T Test*, P = 0:05

Tukey test results obtained probability value between the positive control group with negative group > 0.05 so that it can be stated that there are no differences in mean serum creatinine level methylprednisolone group with distilled water. Besides, the probability value obtained between the positive control group with a cinnamon extract group all doses <0.05 so it can be concluded that there are differences between the mean serum creatinine level methylprednisolone group with all the cinnamon extract group.

Doses of 200 mg/kg body weight to more effectively reduce serum creatinine level compared with a dose of 50mg / kg. The dose of 100 mg/kg body weight to more effectively reduce creatinine levels compared to 200 mg/kg body weight, so it can be concluded that a dose of 100mg / kg was the most effective dose for lowering levels of creatinine in Wistar strain male rats with UUO treatment.

Discussion

Serum creatinine may represent not only a kidney injury, but also a normal response of the kidney to extracellular volume depletion, or a decrease in renal blood flow so that creatinine can be used as a one-parameter in the diagnosis of acute renal disorder also known as acute kidney injury (AKI).^{13,14}

It was found the average serum creatinine before treatment UUO rat amounted 19.92 μ mol / L - 20.81 μ mol / L and after treatment 57.13 μ mol / L - 58.68 μ mol / L. Based upon criteria KDIGO, an increase in serum creatinine indicates acute kidney injury has occurred Stage 2.²

Statiska analysis results showed that all doses of the cinnamon extract can reduce levels of creatinine ($p < 0.05$). Extract of cinnamon (*Cinnamomum burmanii*) can lower serum creatinine levels at doses of 50 mg / kg, 100 mg / kg, 200 mg / kg. After being given a cinnamon extract creatinine serum levels in the rat is 37.53 μ mol / L - 50,87 μ mol / L, which means there is a decrease in battery staging ie from stage 2 to stage 1.

The active compounds such as polyphenols from cinnamon cinnamaldehyde as an antioxidant and anti-inflammatory to reduce levels of serum creatinine. The mechanism whose role is to suppress oxidative stress from a variety of oxidative reactions that occur in kidney.^{16,17,18}

Increased inflammatory mediators such as Cystatin C and interleukin-18, which will further increase the expression of intracellular adhesion molecule-1 and P-selectin on endothelial cells, resulting in increased cell adhesion of inflammatory cells, especially neutrophils. This situation will lead to an increase in oxygen-free radicals, which will cause necrosis of the cells and will improve biomarker creatinine serum.^{19,20}

Increasing doses of the cinnamon extract are not directly proportional to the decrease in serum creatinine levels. Doses of 200 mg/kg body weight to more effectively reduce serum creatinine level compared with a dose of 50mg / kg. A dose of 100 mg/kg body weight to more effectively reduce creatinine levels compared to 200 mg/kg. Lowest creatinine levels are shown in groups of the rat who received therapy cinnamon extract 100mg / kg. This indicates that there has been a steep dose which means an increase in the therapeutic dose not improve the work of active compounds cinnamon extract substances due to the active interaction between the active compounds found in cinnamon. This is because, there is one active compound (diterpene) of cinnamon which is antagonistic so that it can eliminate the anti-inflammatory and antioxidant effect of cinnamaldehyde on cinnamon extract when the dose of cinnamon extract is elevated.^{21,22} cinnamon extract 100mg / kg is effective doses as add-on therapy in the state acute renal insufficiency or MMR. Research is also showing that an extract of

cinnamon is more effective to decrease serum creatinine levels compared with methylprednisolone.

Conclusion

Cinnamon extract dose of 100 mg/kg body weight is an effective therapeutic dose for renal protection in a state of acute kidney injury (AKI) Wistar male rats.

References

1. Wilson L, Sylvia. 2012. Concept Clinical Pathophysiology disease processes. 6th edition, Jakarta: Book Medical Publishers, EGC.p867-889.
2. Kidney Disease Improving Global Outcomes (KDIGO). KDIGO 2012. Clinical Practice Guideline for Acute Kidney Injury. Kidney International Supplements. Vol.2. 19-36,
3. Nash K, Hafeez A, Hou S. 2002. Hospital-acquired renal insufficiency. American Journal of Kidney Diseases. 39: 930-936.
4. Lameire N, Biesen WV, Vanholder R. 2006. The rise of prevalence and the fall of mortality of Patients with acute renal failure: what the analysis of two databases does and does not tell us. J Am Soc Nephrol.17: 923-5.
5. Chevalier, R., Forbes, M. and Thornhill, B. 2009. Ureteral obstruction as a models of renal interstitial fibrosis and obstructive nephropathy. Kidney International, 75 (11), pp.1145-1152.
6. Rismunandar and Farry B. Paimin. 2003 Cinnamon Cultivation and Processing. Sower Swadaya, Jakarta.
7. Tortora, G. and Derrickson, B. 2012. Principle of human anatomy and physiology. 13th ed. John Wiley & Sons, Inc., pp.1065-1107
8. United State Renal Data System (USRDS). 2015 Annual Data Report *Chapter 5: Acute Kidney Injury*. Vol. 1. 57-66
9. Markum, HMS2009. *Acute Kidney Disorders*. In: Sudoyo AW et al (Ed). *Internal medicine textbook*. 5th edition, Jakarta: InternaPublishing.p1041

10. Daswir. 2006. Plant Profile Cinnamon in Indonesia. (Cinnamon spp.). Technology developments Spices and Medicinal Plants. Estate Crops Research and Development Center, Bogor. Vol. 17, No. 1, p. 46.
11. Dalimartha, S. 2009. Atlas Plant Medicine Volume VI. Jakarta: Puspa Swara. Hal: 49-51.
12. Dugoua JJ, Seely, D., Perri, D., Cooley, K., Forelli, T., Mills, E., Koren, G. 2007. From type 2 diabetes to antioxidant activity: A systematic review of the safety and efficacy of common and cassia cinnamon bark. *Canadian Journal of Physiology and Pharmacology* 85: 837-847.
13. De Cássia da Silveira e Sá, R., Andrade, L., Barreto de Oliveira dos Reis, R. and de Sousa, D. 2014. A Review on Anti-Inflammatory Activity of phenylpropanoids Found in Essential Oils. *Molecules*, 19 (2), pp.1459-1480.
14. Stavinoha RC & Vatte DA. 2015. Potential neuroprotective effects of cinnamon. *International Journal of Applied Research in Natural Products*. Vol. 8, No. 3, pp.24-26
15. Kaplan, A. and Szabo, LL 1979. *Clinical Chemistry: Interpretation and Techniques*. Philadelphia: Lea and Febiger.
16. Bellassoued, K., Ghrab, F., Hamed, H., Kallel, R., van Pelt, J., Lahyani, A., Ayadi, F. and El Feki, A. 2019. Protective effect of essential oil of *Cinnamomum verum* bark on hepatic and renal toxicity induced by carbon tetrachloride in rats. *Applied Physiology, Nutrition, and Metabolism*, 44 (6), pp.606-618.
17. Coca, SG, Singanamala, S., Parikh, CR, 2012. Chronic Kidney Disease after Acute Kidney Injury: A Systematic Review and Meta-analysis. *Kidney Int.*81 (5): 442-448
18. Kang, L., et al. 2016. Cinnamaldehyde and allopurinol reduce fructose-induced cardiac inflammation and fibrosis by attenuating CD36-mediated TLR4 / 6-IRAK4 / 1 signaling to suppress NLRP3 inflammasome activation. *Scientific reports*, 6 (1).
19. Kundu, M., Mondal, S., Roy, A., Martinson, J. and Pahan, K. 2016. Sodium Benzoate, a Food Additive and a metabolite of Cinnamon, Enriches Regulatory T Cells via STAT6-mediated upregulation of TGF- β . *The Journal of Immunology*, 197 (8), pp.1-13.

20. Muhammad, D. and Dewettinck, K. 2017. Cinnamon and its derivatives as potential ingredients in functional food-A review. *International Journal of Food Properties*, pp.1-27.
21. Sawhney, S. and Fraser, S. 2017. Epidemiology of AKI: Utilizing Large Databases to Determine the Burden of AKI. *Advances in Chronic Kidney Disease*, 24 (4), pp.194-204.
22. Stavinoha RC & Vatte DA. 2015. Potential neuroprotective effects of cinnamon. *International Journal of Applied Research in Natural Products*. Vol. 8, No. 3, pp. 24-26