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The Efficacy of Cinnamon Extract (*Cinnamomum burmannii*) on Reducing *Staging Acute Kidney Injury* in *Ischemia Reperfusion* (IR) Model

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A R T I C L E I N F O

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A B S T R A C T

Background. Acute kidney injury (AKI) is defined as sudden decline in the glomerular filtration rate, resulting in the retention of nitrogenous wastes, such as urea and creatinine in plasma. Cinnamomum burmannii is known as a anti-inflammatory renoprotective agent, although the precise mechanism is not well understood. This study aimed to elucidate the effectiveness of Cinnamomum burmannii extract in decreasing creatinine level of acute kidney injury Ischemia reperfusion (IR) model. **Method**. We performed Ischemia reperfusion (IR) in male Wistar rat to induce acute kidney injury. The rat (n=30) were divided into six groups: IR, 1 group treated with methylprednisolone as a control (IR+M), 3 groups treated with different oral Cinnamomum burmannii extract doses (50mg/kg (IR+EKM1), 100mg/kg (IR+EKM2), and 200 mg/kg (IR+EKM3), and a Sham operation (SO) group. AKI stage reduction based on serum creatinine levels, before and after modeling, before and after the cinnamon extract intervention. Creatinine levels were quntified by spectrophotometry and analyzed by *SPSS*. **Result**. Cinnamomum burmannii extract lowers creatinine levels; significant (P <0.05). 200 mg / kgbb is the effective dose of lowering creatinine levels in the IR model. **Conclusion.** Cinnamomum burmannii extract reduced serum creatinine levels associated with decreased acute renal staging in the IR model.

1. Introduction

Acute Kidney Injury (AKI) can be defined as a decrease in quickly and suddenly the kidney filtration function. This situation is characterized by an increase in creatinine concentration. The Acute Kidney Injury Network (AKIN) criteria define AKI as "an abrupt reduction in kidney function within 48 hours, currently defined as an absolute increase in serum creatinine of either ≥ 0.3 mg/dL (≥ 26.4 mmol/L), a percentage increase of ≥ 50% (1.5 fold from baseline), or a reduction in urine output (documented oliguria of < 0.5 mL/kg/hour for > 6 hours)". The increase in the incidence of AKI is associated with an increase in the sensitivity of the AKI diagnostic criteria. Several reports in the world show that the incidence varies between 5%-20% in the community, 20% to 50%% in hospitalized patients, to 20% in patients admitted to the intensive care unit (ICU), with reported mortality rates from around the world range from 25% to 80%. Epidemiologic studies have demonstrated that AKI frequently develops into chronic kidney disease and is a major risk factor of end-stage renal disease.[1-5]

Ischemia/reperfusion injury (IR) is defined by restriction of blood supply to an organ followed by restoration of blood flow and re-oxygenation. IR contributes to pathological conditions called *acute kidney injury* (AKI) that is a clinical syndrome with rapid kidney dysfunction and high mortality rates. The pathophysiology of IR in kidney is very complex but some pathological pathways such as activation of neutrophils, release of *reactive oxygen species* (ROS)

and other inflammatory mediators including adhesion molecules and a variety of cytokines are involved.[6-7]

Cinnamomum burmannii is known to have a role in anti-inflammatory renoprotective effect. Some mechanisms of *Cinnamomum burmannii* action targeting acute kidney injury treatment have been investigated, but further research is necessary to clarify the precise action mechanism. *Cinnamomum burmannii* has high flavonoid and polyphenol content as an anti-inflammatory and used to repair body cells and treat various disease conditions.[8] Nevertheless, its anti-inflammatory effect in renal cells would be interesting to elucidate. Therefore, in this study, we focused on elucidating the effect of *Cinnamomum burmannii* on renal, especially creatinine level as an underlying diagnosis of acute kidney injury.

2. Methods

Cinnamomum burmannii extract

Cinnamomum burmannii is macerated with 96% ethanol solvent at room temperature soaked in a chocolate bottle. After three days of soaking is filtered, the filtrate is stored while the residue is soaked again in the same solvent. This treatment was repeated five times. The filtrate was collected and then evaporated the solvent with a rotary vaccum evaporator (at 50^{o}C) until a thick extract was obtained. Furthermore, the viscous extract is dehydrated using a freeze-dryer to obtain dry extract.

Animal subjects

Wistar rat male (n = 30) age 8 weeks old, with 150–200 gr body weights were obtained from the Experimental Animal Care Unit of Sriwijaya University. Rat were housed in a cage owned by the Department of Anatomy, Faculty of Medicine, Sriwijaya University, with a light-dark cycle of 12:12 hours. We performed IR to induce acute kidney injury. Briefly, rat were anesthetized with biophentyl (0.1mg/kg body weight). The abdomen was opened in the right-flank region. The arteri and vena renalis was visualized and then ligated 30 minute. A sham operation (SO) procedure was used for the control group with the same procedure except for ligating. Subjects were divided into six groups, that is, SO (sham-IR + aquadest), IR (IR + aquadest), 1 group treated with methylprednisolone as a control (IR+M), 3 groups treated with different oral Cinnamomum burmannii extract doses (50mg/kg (IR+EKM1), 100mg/kg (IR+EKM2), and 200 mg/kg (IR+EKM3). Rat got standard chow and free access to water ad libitum. Rat were terminated at day14 after the operation.

Creatinine Analysis by spectrophotometry

The blood of the rat was taken by cutting the neck vein and then collected it in a test tube. Let the blood rest for 15 minutes, then centrifug the blood for 10 minutes at a speed of 3000 rpm to obtain serum. As much as 0.5 mL of pipetized serum is put into a test tube then mixed with 1 mL of working reagent solution. Measurements were made using a UV spectrophotometer (Microlab 200) at a wavelength of 505 nm, in order to obtain serum creatinine levels. The absorbance measurement of the sample was carried out in the first minute after mixing to obtain AS1. The measurement was then continued after 2 minutes from the first measurement in order to obtain AS2. Absorbance measurements were carried out in the same way for standard solutions to obtain Ast1 and Ast2.

3. Results

The probability value for the cinnamon extract group at all doses was <0.05, this indicates that there were differences in the mean creatinine levels in the cinnamon extract group at the dose of 50mg/kg, 100mg/kg and 200mg/kg which also showed the decrease in creatinine level at three doses. The highest decrease of creatinine was found in cinnamon extract 200mg/kg, so it could be stated that the group that was most effective in reducing creatinine level was the group of rat that were given 200 mg / kgBB *Cinnamomum burmannii* extract.

The mean serum creatinine of rats before IR treatment was 0.37 mg / dl. The creatinine level in the blood increased by 2.73 mg / dl after IR. Based on KDIGO criteria, the increase in serum creatinine

indicates a stage 2 acute kidney injury. After being given *Cinnamomum burmannii* extract, the serum cretainine level in rats was 0.62 mg/dl , which means that there is a decrease in AKI, from stage 2 to stage 1.

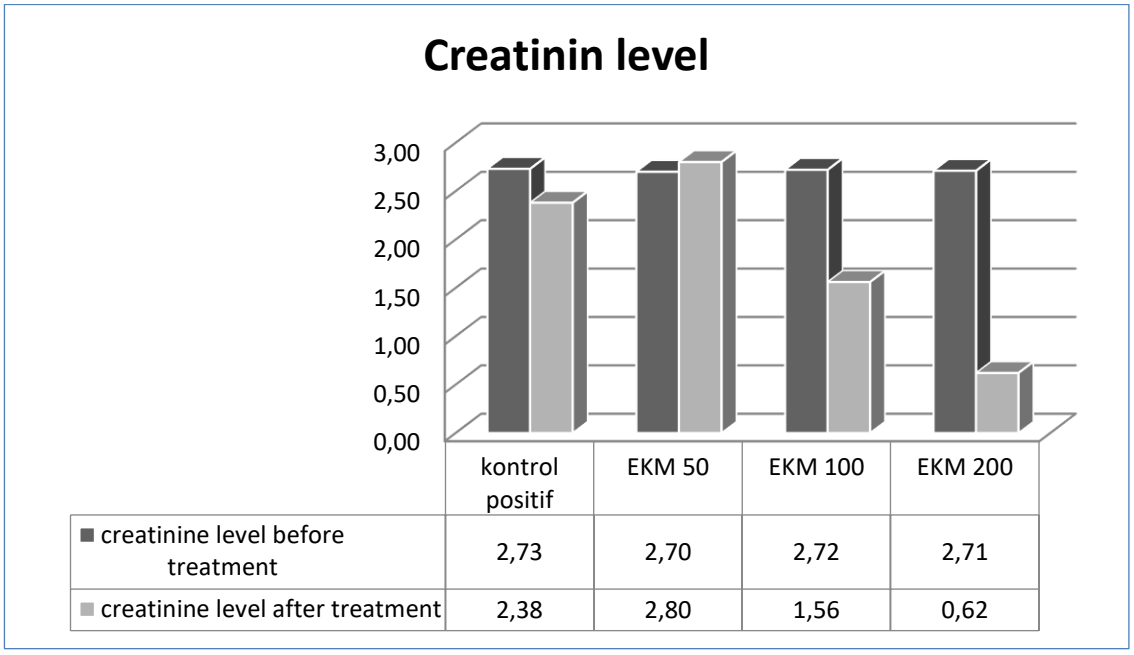

Figure 1. Effectiveness of Cinnamomum burmannii extract on creatinine levels on IR model

4. Discussion

Creatinine levels in the blood indicate injury to the kidneys and the kidney's normal response to extracellular volume depletion and decreased renal blood flow. Thus creatinine can be used as a parameter in diagnosing acute kidney injury (AKI). During IR that lead to AKI, the damaged tissue produce excessive amount of reactive oxygen species (ROS) cause oxidative stress which changes mitochondrial oxidative phosphorylation.[9-11] The blood flow during reperfusion phase of IR can produce oxygen free radicals which leads to lipid peroxidation as main pathway of free radical tissue injuries. Formation of free radicals develops renal tissue injury via peroxidation of membrane lipids and oxidative damage of proteins and DNA contribute to apoptosis and cell death.[12-13] Also the down regulation of the antioxidant enzyme system such as catalase, superoxide dismutase, and glutathione peroxidase could be responsible for the pathophysiology of ischemia-reperfusion injury.[14] Therefore inhibiting this pathway or prevention of free radical production is the strategy to protect the tissue during IR.

Recent attentions to herbal products encourage scientists to investigate natural agents on IR. Most of these products exert renoprotective effects on IR by the radical scavenging and anti inflammantory activities such as *Cinnamomum burmanii*. It contains active chemical compounds such as flavonoids, phenols, terpenoids and cinamaldehyde. Flavonoids are secondary metabolite compounds found in green plants. Flavonoids including natural phenolic compounds that have potential as anti-inflammatory and antioxidants. The benefits of flavonoids include protecting cell structures, increasing the effectiveness of vitamin C, anti-inflammatory, preventing bone loss and as an antibiotic. The effect of flavonoids as antioxidants also indirectly supports the anti-inflammatory effect of flavonoids. Flavonoids and cinnamaldehyde can increase the glomerular filtration rate (GFR) by reducing reactive oxygen species (ROS) that cause oxidative stress in the kidneys. Increased renal glomerular filtration rate can lead to increased

creatinine excretion so that creatinine levels in the blood will decrease.[15-16] The use of medicinal plants is effective because it has low side effects compared to modern medicines.

5. Conclusion

This study showed the beneficial effect of *Cinnamomum burmanii* supplementation in acute kidney injury conditions through reduction of creatinine level . Following study about adding *Cinnamomum burmanii* supplementary therapy to AKI ambulatory therapy will be needed to adjust those effects in clinical use. We also need further study to understand the precise mechanism of *Cinnamomum burmanii* in both the classical and non-classical pathways in reactive oxygen species (ROS) cause oxidative stress and other potential cells of renal injury.

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