Turnitin Renoprotective effect of sambiloto

by Dwi Retnoningrum

Submission date: 07-May-2023 06:54PM (UTC+0700)
Submission ID: 2086419869
File name: 17286-62697-1-PB.pdf (281.33K)
Word count: 4194
Character count: 22992

Indexed by : DOAJ Google Crossref Dimension sinta GARUDA

J.Biomed.Transl.Res
ISSN: 2503-2178

JOURNAL OF BIOMEDICINE AND TRANSLATIONAL RESEARCH

Available online at JBTR website: https://jbtr.fk.undip.ac.id

Original Research Article

Renoprotective Effect of Sambiloto (Andrographis Paniculata) Leaf Extract on Lipopolysaccharide – Induced Septic Rats

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Article Info
History
Received: 27 Jan 2023
Accepted: 03 Mar 2023
Available: 30 Apr 2023

Abstract

Background: Acute kidney injury (AKI) is one of organ dysfunctions related to sepsis. AKI may be mediated by uric acid, and blood creatinine levels can be utilized to diagnose the condition to measure kidney function. Sambiloto (Andrographis paniculata) is a traditional medicine that has flavonoid compounds that can reduce creatinine levels and Xanthine Oxidase Inhibitors which can reduce uric acid levels.

Objective: Septic model rats generated by lipopolysaccharide were used to test the effects of sambiloto (Andrographis paniculata) leaf extract on serum creatinine and uric acid levels (LPS).

Methods: This study was experimental employing 25 rats split into 5 groups as the post-test alone control group: healthy control with standard feed (HC), negative control with LPS injection(NC), Treatment (T)1 (A.Paniculata 200 mg/kgBW+LPS), T2(A.paniculata 400 mg/kgBW+LPS), and T3(A.paniculata 500mg/kgBW+ LPS). A.paniculata leaf extract was given via oral gavage on day 8-21. An intraperitoneal injection of LPS 5 mg/kgBW was given on day 22. On the 25th day, the blood serum was analyzed for creatinine levels using the Jaffe method, and uric acid was analyzed using the enzymatic photometric method. One-way analysis of variance (Kruskal-Wallis) and the Kruskal-Wallis test were used to evaluate the data.

Results: The mean creatinine levels of the HC, NC, T1, T2, and T3 groups were 0.7±0.01;3.5±0.04;2.9±0.03;1.9±0.05; 1.3 ±0.04 mg/dl respectively. The mean uric acid levels of the HC,NC,T1,T2, and T3 groups were 1.7±0.05;8.2±0.11; 4.5±0.03;4.0±0.12;3.0±0.19 mg/dl respectively. There were significant differences *(p<0.05)* in creatinine levels in groups T2*(p=0.031)* and T3*(p=0.001)* to NC group and serum uric acid levels in groups T1*(p<0.001)*, T2*(p<0.001)*, and T3*(p<0.001)* to NC group which creatinine and uric acid levels were lower than NC group.

Conclusion: Andrographis paniculata leaf extract has a renoprotective effect against AKI in LPS-induced septic rats

Keywords: *Andrographis paniculate; creatinine; uric acid; lipopolysaccharide; AKI; sepsis*
Permalink/ DOI: https://doi.org/10.14710/jbtr.v9i1.17286

INTRODUCTION

Sambiloto (Andrographis paniculata) is one of medicinal plants that can thrive and has been cultivated in various parts of the world, including in Indonesia.[1] In Indonesia, sambiloto is marketed either in a single preparation or in combination with other natural ingredients in tablet dosage form.[2] It has been recognized that Sambiloto has antipyretic, analgesic, nephroprotective, antibacterial, anti-inflammatory, and immunostimulating properties.

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In addition, sambiloto contains bioactive compounds found in plants; including alkaloids, flavonoids, andrographolides, glycosides, saponins, steroids, tannins, diterpenes, and more.[3]

Flavonoids are among the compounds found in sambiloto. A broad class of polyphenolic chemicals, flavonoids have a benzo—pyron structure.[4] Flavonoids have antimicrobial, antioxidant, anti-inflammatory, and anti-diabetic properties in the medical field.[5] In addition, flavonoids are able to increase the glomerular filtration rate (GFR). An increment in the glomerular filtration rate might lead an increment of creatinine level which was excreted in the kidneys, in order to reduce creatine levels in the blood.[6]

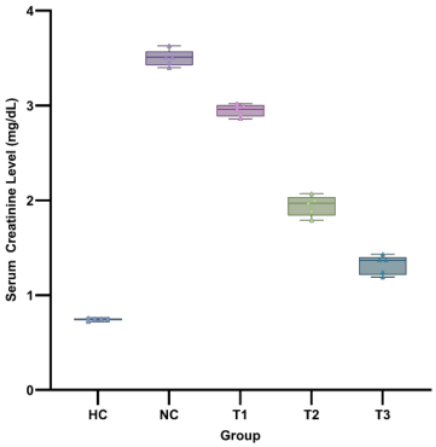

Figure 1. Box plot graph of serum creatinine levels

Sepsis is a life-threatening multi-organ dysfunction caused an abnormal immune response to infection.[7] This condition, known as sepsis, by endotoxins such as lipopolysaccharides (LPS).[8,9] The bacterial Gram-negative bacteria have a cell wall that is mostly made up of lipopolysaccharides (LPS). Toll-like receptor 4 (TLR4) transmembrane protein activity can be boosted by lipopolysaccharides. The TLR4 receptor makes use of the infrastructure of MD-2 protein to bind with receptors on lipopolysaccharides.

The process of presentation lipopolysaccharide to MD-2 may also be facilitated CD14 and LBP, among other proteins. Upon activation, TLR4 signals for the recruitment MyD88, Mal, Trif, and Tram are examples of intracellular adaptor molecules that indicate the activation of other molecules. The IRAK1, IRAK4, TBK1, and IKKi protein kinases may be activated as a result, allowing for a more robust signaling system and the activation or repression of genes that affect how the body reacts to inflammation.[10]

One way that kidney function is evaluated is by monitoring the creatinine level in the blood.[11] Renal function loss can occur for a variety of reasons, including An abrupt Injuries to the kidneys that happen suddenly can cause a drop in kidney function known as acute renal injury (AKI) various etiologies and pathophysiological processes. [12] Up to 50% of mortality in intensive care unit patients are attributed to septic endotoxemia, which is often accompanied with AKI. The death rate for patients with AKI caused by sepsis was greater than that of those without sepsis. The main ingredient of the endotoxin produced from wall of Gram-negative bacteria is lipopolysaccharide (LPS), and it is primarily responsible for causing endotoxemia. Lipopolysaccharides activate the renal inflammatory cascade, which leads cause a cascade of inflammatory cytokines to be released, wreaking havoc on the kidneys an advanced state. [13] Sepsis-related AKI is characterized by impaired glomerular filtration, elevated serum urea and creatinine levels, and acute tubular necrosis as a result of hypovolemia and poor tissue blood perfusion.[14]

Recently, it found out that uric acid is a potential mediator of AKI.[15] Uric acid stimulate inflammatory pathways that can exacerbate the incidence of AKI through crystalline and non-crystalline mechanisms.[16,17] Urine supersaturation, urate crystallization, and tubular lumina obstruction are just a few of the problems that might begin due to an increase in uric acid excretion, all of which can lead to localized granulomatous inflammation involving macrophages and T cell infiltration.[18] In previous studies, it was found the existence of Xanthine Oxidase Inhibitors in flavonoids. The structure of benzopyran contributes to XO inhibition which can affect uric acid levels in the blood.[19]

Research shows that was an effect of giving a graded dose of sambiloto extract with kidney function, namely creatinine and uric acid in Wistar rats induced by lipopolysaccharide. The doses of sambiloto extract used in this study were 200, 400, and 500 mg/kgBW.

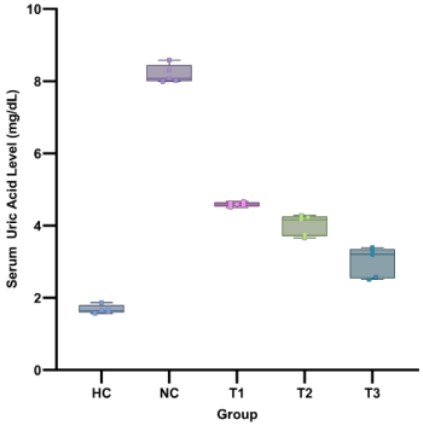

Figure 2. Box plot graph of serum uric acid levels

MATERIALS AND METHODS

We employed a true controlled experiment with a single post-test condition to conduct this analysis. From June through August of 2021, this study was conducted on male Wistar rats between the ages of two and three months. On May 24, 2021, The Medical Faculty at Diponegoro University's Research Ethics Commission issued protocol number 50/EC/H/FK-UNDIP/V/2021,

indicating that the study was given the green light from an ethical standpoint.

Twenty-five rats were split into five groups at the Experimental Animal Laboratory of PSPG Gadjah Mada University: the healthy control group (HC), which received only standard feed; the negative control group (NC), which received standard feed and an injection of lipopolysaccharide (5 mg/kgBW) on day 22; in addition to the First, Second, and Third Group Treatment (T1, T2, and T3), which received standard feed and sambiloto leaf extract (200, 400, or 500 mg/kgBW (on day 8th – 22th), and injected with lipopolysaccharide 5 mg/kgBW on day 22. The inclusion criteria in this study were healthy male Wistar rats weighing 150-200 grams and 2-3 months of age while the exclusion criteria were rats with anatomical abnormalities, and the dropout criteria were weight loss of rats after the adaptation period, dead rats or illness rasts during the experiment. On 25th days, each group was terminated using chloroform and blood samples were taken to measure creatinine levels using the jaffe method and uric acid using the enzymatic photometric method.

Data of creatinine and uric acid levels were analyzed using a computer program. After completing a descriptive analysis, the data normality was subjected to the Shapiro-Wilk test for validity. The Kruskal-Wallis test was used for the statistical analysis because the creatinine data did not have a normal distribution, while the uric acid data followed a normal distribution, and the ANOVA one-way test was utilized to complete the study. It can be said the results is significant if there is a difference with a p value ≤ 0.05.

RESULTS

All rats were found to be alive and there is no rats with dropout criteria were found until the end research period. Data on creatinine and uric acid levels were tested for normality with the Shapiro-Wilk. Based on the normality test, data on serum creatinine levels were not normally distributed ($p<0.05$) in one group serum uric acid levels exhibited normal distribution ($p> 0.05$), therefore the study proceeded with Other variables were examined using the Kruskal-Wallis and Mann-Whitney tests, parametric test of association (one-way ANOVA) and post-test non-parametric tests. The mean creatinine levels of the HC,NC,T1,T2,T3 were 0.7±0.01;3.5±0.04;2.9±0.03;1.9±0.05; 1.3 ±0.04 mg/dl respectively. The mean uric acid levels of the HC,NC,T1,T2, and T3 groups were 1.7±0.05;8.2±0.11; 4.5±0.03;4.0±0.12;3.0±0.19 mg/dl respectively.

Based on the Levene homogenity test, the significance of data based on the median of the data on serum uric acid levels was 0.000 (<0.05) so it can be concluded meaning that uric acid levels in the blood can fluctuate level data in five groups was not homogeneous.

Results from Using the Kruskal-Wallis test, a discernible variation in serum creatinine concentration was seen, with a significance level of 0.000 (p0.05). The Mann Whitney test results for HC-NC, HC-T1, HC-T2, HC-T3, NC-T1, NC-T2, NC-T3, T1-T2, T1-T3, and T2-T3 were 0.000, 0.001, 0.031, 0.282, 0,282, 0.031, 0.001, 0.282, 0.031, and 0.282 respectively. There is a statistically significant variation according to the analysis of variance finding of 0.000 in serum uric acid levels (p0.05). The post hoc analysis results of serum uric acid levels for HC-NC, HC-T1, HC-T2, HC-T3, NC-T1, NC-T2, NC-T3, T1-T2, T1-T3, and T2-T3 were 0.000, 0.000, 0.000, 0.000, 0.000, 0.000, 0.000, 0.002, 0.000, and 0.000 respectively.

DISCUSSION

The increment in serum creatinine levels in rats which had been administered with lipopolysaccharide injection against healthy controls indicates that the administration of lipopolysaccharide injection induced decline in renal function, manifested by an increase in blood creatinine levels. Endotoxin is an outer membrane protein produced through the involvement of When sepsis first sets in, gram-negative bacteria play a role. Research on sepsis has made extensive use of the LPS injection model. An increase in inflammation-inducing such cytokines as TNF-alpha and IL-1 other early clinical signs of sepsis, are triggered by LPS administration, although there is no bacteremia.[20]

What we call "sepsis" is actually a variety of organ failure brought on by an abnormal immune response to infection.[7] Gram-negative bacteria have an outer membrane is made of LPS. To do this, they bind to a lipid called lipid A. (the bioactive portion of LPS), LBP in the blood and extracellular fluid transports LPS to clusters of differentiation14 (CD14) on monocytes, macrophages, and neutrophils. To further increase the creation and release of inflammatory mediators, the LBP-LPS complex interacts with the CD14 receptor, generating LPS binding to TLR4. In addition, Proinflammatory cytokines stimulate endothelial cells by increasing the expression of adhesion receptors, allowing for the adherence of neutrophils, monocytes, macrophages, and platelets. When these cells are activated, they secrete endothelium-damaging mediators such as proteases, oxidants, prostaglandins, leukotrienes and contribute to increased permeability, vasodilation, and an imbalance between the procoagulant and anticoagulant systems. Nitric oxide (NO), a powerful vasodilator that can lead to sepsis, is produced in excess when iNOS activity is high.[21] The rats model with systemic lipopolysaccharide induction was the most widely used in researches with sepsis rat model.[7]

The leading cause of Acute Kidney Injury is sepsis (AKI) through various mechanisms, some of which are inflammation, microvascular dysfunction, and metabolic reprogramming.[22] A number of tubular transporters in the kidney, such as sodium/hydrogen exchanger 1, are directly inhibited by lipopolysaccharides (NHE1).[23] This mechanism promote serum creatinine levels which indicate impaired kidney function, especially in glomerular filtration function. [24]

Results from this study demonstrate that serum creatinine T2 and T3 therapy groups had significantly lower levels than the control group when compared to serum creatinine levels in the NC group which was only given lipopolysaccharide injection. Based on previous research, the administration of sambiloto leaf extract has a renoprotective effect on Acute Kidney Injury.[25] It has been shown that the flavonoid compounds contained in Andrographis paniculata was able to increase the glomerular filtration rate (GFR).[5] Over time, the kidneys were able to process the extra creatinine produced as a

result of an increase in GFR, lowering blood creatinine levels.[6]

T3 subjects fared worse than the healthy controls. showed no discernible deviations. This shows that the T3 group's creatinine levels dropped after being given sambiloto leaf extract at 500 milligrams per kilogram were almost similar with the healthy control group. Previous studies had shown that sambiloto leaf extract had an effect on oxidative stress at a dose of 500mg/kgBW and renoprotective effect on Wistar rats.[25,26]

The rats that were administered with lipopolysaccharide injection show an increment in serum uric acid levels against healthy controls, this result indicates that the administration of lipopolysaccharide injection induce a severe condition of inflammatory on rats that could cause sepsis. It has recently been recognized that uric acid is hypothesizes that this biological component may promote an inflammatory response that may exacerbate AKI and hence be considered a mediator of AKI.[16] Evidence from prior research indicates that there are fundamental changes in the renal blood vessels due to the presence of hyperuricemia. Uric acid was found by Ryu et al. to inhibit E-cadherinine epithelial cell expression, leading to a reduction in cell-to-cell contact in rat renal tubular cells. Cell-to-cell communication between epithelial cells is essential for the coordinated secretion of nitric oxide and other chemicals that improve renal blood flow. Moreover, prior research employing proximal tubular epithelial cells from normal adult male kidneys demonstrated that increased uric acid levels generate NAPDH-dependent oxidative alterations that can promote apoptosis. The link between hyperuricemia and tubulointerstitial renal injury is clarified by these results.[27]

Study from S´anchez-Lozada et al. determined that renal biopsy results of Afferent arterioles in rats with high serum uric acid levels were thickened. Arteriole thickness reduces blood flow to the kidneys, which leads to kidney disease. Endothelial function serum uric acid levels were reported to increase after xanthine treatment oxidase inhibitors.[16]

Results from previous study show that the administration of sambiloto leaf extract has a renoprotective effect in Acute Renal Failure.[25] Purine metabolism relies on xanthine oxidase, an enzyme that catalyzes the hydroxylation of hypoxanthine to xanthine as a further results in generating uric acid.[28]

Compared to rats in the control group that received simply an injection of lipopolysaccharide, those in the treatment group that received Andrographis paniculata levels of uric acid in the blood were dramatically reduced in those who took the extract. The uric acid The treatment group's levels were dramatically lower than the control group's. Flavonoids' health benefits have been well-documented for some time contained in Andrographis paniculata has an ability to inhibit Xanthine Oxidase enzymes both competitively and non-competitively. Aliphatic chain substitution found in flavonoids increase hydrophobic interactions and bind tightly to binding sites.[28] Moreover, the sambiloto extract can inhibit xanthine oxidase activity so that it can reduce serum uric acid levels.[29]

Histopathological and immunohistochemical analyses of Sambiloto (Andrographis Paniculata) leaf extract profile of sepsis-induced AKI is required to confirm to the advantage of Sambiloto (Andrographis Paniculata) leaf extract to prevent the sepsis-induced -AKI. Histopathological findings associated with Sambiloto (Andrographis Paniculata) leaf extract administration on sepsis-induced AKI may aid in gaining a deeper comprehension of disease pathways, increasing specificity of data, and improving the efficacy of treatment plans.

CONCLUSION

The present study suggests that Sambiloto (Andrographis Paniculata) leaf extract administration for fourteen days in dose 400 and 500 mg/kgBW as pretreatment before sepsis-induced -AKI exerts significant renoprotective effects in A Sepsis Model in Rats -induced -AKI.

ACKNOWLEDGEMENT

The authors are grateful to the Faculty of Medicine, Diponegoro University for the support provided under research grant no.1664/UN7.5.4.2/PP/2021

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