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Research Article

EFFECTIVENESS AND MECHANISM OF PHYSICIAN HERBS FROM KALI PUTIH BATUR BANJARNEGARA CENTRAL JAVA AGAINST DIABETIC NEPHROPATHY

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ABSTRACT

Objectives: Complications in the kidneys (nephropathy) are one of the chronic complications of diabetes mellitus (DM) most common microvascular and estimated to reach 30–40% of all sufferers of DM. Until now there is no cure drug that can prevent diabetic nephropathy. Therefore, the handling of this issue should be done seriously, one of them through an exploration of drug discovery and drug material. Ristoja in 2015 in the ethnic Javanese Banyumasan successfully explores the types of plants, herb, and traditional medicine culture. One is conducted by the Kaliputih Traditional Medicine, Batur, Banjarnegara, Central Java. Based on the results of the interview, traditional medicine has herb for disease therapy kidney failure which consists of 11 species of plants.

Methods: The herbs were extracted by infundation method. Sprague Dawley albino male rats were divided into 3 groups (normal, positive, and negative) and 3 sample test groups with 3 different doses (18, 36, and 54 mL/kg body weight [BW]) previously induced streptozotocin. Observations were carried on the levels blood urea nitrogen (BUN), creatinine, uric acid, and nuclear factor kappa B (NF-κB), cyclooxygenase-2 (COX-2), and transforming growth factor-beta (TGF-β) kidney immunohistochemically and histology analysis.

Results: Statistical results showed a significant increase of BUN levels in all dose variation groups after being given herbs, compared to the negative control group. The result of the examination of biochemical parameters of creatinine levels statistic showed significant ($p<0.05$) decrease in the dose 18 and 36 mL/kg BW compare with the negative group. The result of the study on histopathology kidney organs there are are damages to each test in each organ that is necrosis. The result of NF-κB, COX-2, and TGF-β expression no significant decrease compared with the negative controls.

Conclusion: The herbs are not capable of nephropathy diabetic and need more research to know that activity as nephroprotective.

Keywords: Diabetic nephropathy, Herbs, Traditional medicine.

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INTRODUCTION

Diabetes mellitus (DM) is a chronic disease that impacts on morbidity and mortality [1]. Microvascular and macrovascular complication is a major problem on the DM patients [2]. Complications in the kidneys (nephropathy) are one of the chronic complications of DM most common microvascular [3,4] and estimated to reach 30–40% of all sufferers of DM [5]. Pathophysiology of the onset of nephropathy involving hemodynamic and metabolic causing hyperglycemia and hyperlipidemia glucotoxicity trigger lipotoxicity in the kidney. High blood glucose in the kidney triggers the occurrence of inflammation and oxidative stress due to the increased production of reactive oxygen species (ROS). This can lead to hypoxia and nephropathy [6].

The main therapy for the prevention of nephropathy is controlling the levels of glucose and lipids in the blood. In addition, the use of antioxidants will suppress the production of ROS, and prevent the occurrence of oxidative stress thus preventing nephropathy [6]. Until now, there is no cure drug that can prevent diabetic nephropathy. Therefore, the handling of this issue should be done seriously, one of them through an exploration of drug discovery and drug material. The 56th World Health Assembly issued the resolution to countries member of the World Health Organization to enhance the research of traditional medicine as well as ensure the quality, safety, and efficacy herbal medicine by setting standard of traditional medicine [7].

Riset tanaman obat dan jamu (Ristoja) in 2015 in the ethnic Javanese Banyumasan successfully explores the types of plants, herb, and traditional medicine culture. One is conducted by the Kaliputih Traditional Medicine, Batur, Banjarnegara, Central Java. Based on the results of the interview, traditional medicine has herb for disease therapy kidney failure which consists of 11 species of plants; *Strobilanthes crispus* as an antidiabetic [8], *Orthosiphon aristatus* as a nephroprotective [9], *C. arabica* can decrease creatinin [10], *Beta vulgaris* as cholesterol-lowering [11], *Saccharum officinarum* as a high-density lipoprotein enhancer [12], *Canna edulis* can decrease creatinine levels [13], *Curcuma xanthorriza, Curcuma mangga,* and *Curcuma domestica* as an antioxidant, anti-inflammation and nephroprotective [14], and *Averrhoa bilimbi* as antihyperlipidemic [15] and srintil hutan that unknown morfo-anatomy or Latin name.

MATERIALS AND METHODS

Materials

The herb of Kaliputih, Batur, Banjarnegara, Central Java used empirically for the therapy of renal failure. Streptozotocin kit, ureum kit, creatinin kit, uric acid kit, blood urea nitrogen (BUN) kit, antibodies of transforming growth factor-beta (TGF-β), NF-kB, and cyclooxygenase-2 (COX-2). Citrate buffer pH 4.5, ethanol, 3,3′-diaminobenzidine staining, xilen, hydrogen peroxide, pioglitazon were used.

Instrumentation

Spectrophotometer UV-vis (Shimadzu, Japan), Rotary evaporator R–144 (Buchi Labortechnik AG, Switzerland), 100–1000 µl micropipette (Eppendorf) were used.

Methods

The herb that will be tested is provided based on information from physician of Kaliputih and taken directly from physician domicile. Herbs were determined in Biology Laboratory of Universitas Ahmad Dahlan, Yogyakarta, Indonesia, and numbered 092/lab.bio/B/VII/2018. All the ingredients washed clean, pounded, and boiled with 2 liters of water to half. Sparaguey Dawley rat males, 8 weeks (220–260 g) obtained from Badan Pengawas Obat dan Makanan. Before used, rats acclimated in cages for 1 week. The rat was weighed and grouped randomly into six groups, and each group consists of 5 rats. In Group II–VI rats were inducted with streptozotocin dose of 40 mg/kg, whereas rats of Group I were just given per oral (po) the saline solution. The induced rats were observed to gain information on the increasing level of blood sugar for 1 week.

Activity test of herbal drink

Rat with blood sugar levels of >350 mg/dL were included in testing. Group I was a normal control (given saline peroral). Group II was a negative control (streptozotocin). Group III was the positive control (given a streptozotocin and pioglitazon 2.4 mg/kg po). Groups IV, V, and VI in a row were given herbs treatment doses of 18, 36, and 54 mL/kg po after being given the streptozotocin. The treatment was given for 15 days in accordance with the therapy conducted by physician. For 15 days, the signs of DM as the amount of water intake, food, weight, urine pH, and volume of urine were observed. Fasting blood sugar levels were determined on a day-to-0, 7^{th}, and 15^{th} using a spectrophotometer with a kit of glucose.

Examination of blood biochemical parameter using spectrophotometer UV-vis

Examination of biochemical parameters using blood serum was taken from vena jugularis. Measured parameters include blood glucose levels and renal function (BUN, creatinine, and uric acid levels) using spectrophotometric Microlab 300. Total of 10 µL serum was added with the reagent kit and prepared according to the kit procedure

Examination of histopathology organ

After the blood was taken, the rats were sacrificed for the kidney. Histopathology examination was conducted at the Veterinary Faculty of Gadjah Mada University.

Immunohistochemical organ

Immunohistochemical analysis of TGF-β, NF-kB, and COX-2 of kidney was conducted at the Veterinary Faculty of Gadjah Mada University.

Ethical considerations

Ethical approval was granted by the Ethics Committee, Universitas Ahmad Dahlan, Yogyakarta, Indonesia, number 011609136.

Statistical testing

The resulted data were quantitative, qualitative, and semi-quantitative data. Quantitative and semiquantitative data were tested preliminarily with Kolmogorov–Smirnov for normality and Levene Test for homogeneity. Parametric data were tested with ANOVA followed by t-test, while non-parametric data were tested with Kruskal–Wallis followed by Mann-Whitney test. Meanwhile the qualitative fund was conducted through descriptive analysis. The statistical level of significance was set at 95% ($p<0.05$).

RESULTS AND DISCUSSION

Measurement of blood biochemical parameters spectrophotometer UV-vis

The result is as illustrated in Kintoko *et al.*, where there is a significant rise in glucose levels of the animals, before and after the test that inducted streptozotocin that animals which had increased blood glucose levels by streptozotocin were given renal failure for 15 days. The results show a significant decrease in the dose of 36 and 54 mL/kg body weight (BW) compared with the negative control group [16].

Before testing, streptozotocin-induced to obtain diabetic rats. In this study, a dose was used to induce the test animals through intraperitoneal at 40 mg/kg [17]. After 1 week, the rats will make a disruption of the response to glucose and the sensitivity of β cells to glucose. From the results of previous research by Kintoko *et al.* that blood glucose level of test animals, there is a significant increase of blood glucose level after induced streptozotocin dose 40 mg/kg BW [16].

Streptozotocin is widely used as diabetic nephropathy. However, it could also be cytotoxic to kidneys making it difficult to distinguish between diabetic-related nephropathy and streptozotocin-induced nephropathy. One study reported that the streptozotocin-induced diabetic rat was not suitable for long-term studies because of progressive renal tumorigenesis. In addition, weight loss, respiratory distress, and rapid glycemic shifts resulting in life-threatening hypoglycemia. Nephrotoxicity in the form of transient proteinuria, azotemia, abnormalities of tubular function, and acute renal failure was described as squamous metaplasia may be an important part of streptozotocin renal toxicity [18]. However, Evan *et al*. reported that, in contrast with alloxan, streptozotocin caused no detectable renal injury at the dose of 60 mg/kg which was approximated as the one we used [19].

Renal function test (Table 1) was to measure the levels of BUN, uric acid, and creatinine in blood. Statistical results showed a significant increase of BUN levels in all dose variation groups after being given herbs, compared to the negative control group. On examination of creatinine levels statistic showed significant decrease in the dose 18 and 36 mL/kg BW compare with the negative group. Serum uric acid was not significantly different between hyperglycemic and healthy control groups.

Measurement of BUN, creatinine and uric acid levels to see parameters of renal function induced by streptozotocin and given renal failure with three different doses in Table 1. On examination of uric acid levels that may affect 3 groups comparable to normal controls and controls negative. On examination of BUN levels, there was a significant increase of 3 groups using negative controls. This increase in BUN is similar to that of Adam *et al.* in which *O. stamineus* can significantly increase glucose, albumin, urea and creatinine levels. Elevated BUN levels are triggered because *O. stamineus* plant has an effect as a diuretic. The diuretic effect can be affected by the high electrolyte effect of the herb and leading to the renal epithelium. Diuretic activity will inhibit water reabsorption to the tubular epithelium. The active compound of the *O. stamineus* plant is known to have an effect as a diuretic such as flavonoids glycosides and saponins [20].

Table 1: Results of renal function parameters measurements

Treatment	BUN (mg/dL)	Uric acid (mg/dL)	Creatinine (mg/dL)
Normal control	179.05±55.43	5.12±0.57	14.65±4.58
Negative control	280.27±123.95	4.43±0.88	33.47±21.22
Positive control	231.79±36.6	4.55±1.06	11.03±2.75
Dose 18 mL/kg BW	329.63±59.95#	4.79±0.45	18.3±7.41#
Dose 36 mL/kg BW	321.98±109.54#	3.77±0.57	18.98±8.88#
Dose 54 mL/kg BW	363.1±134.38#	4.41±1.26	21.82±5.19

All the data were shown at the mean ± SD, n=5. *Significant different from normal control group, $p<0.05$. #Significant different from negative control group, $p<0.05$.
SD: Standard Deviation, BUN: Blood Urea Nitrogen, BW: Body Weight.

At the creatinine level, 3 test groups were compared with normal control and negative control. There was a significant decrease in the dosage of 18 and 36 mL/kg BW herbs compared with the negative controls. Decreased levels of creatinine caused flavonoids contained in some mixture of herbs. The use of water solvent in the preparation of the herb increases the solubility of flavonoids. In addition, the curcumin content of some plants of the Curcuma genus that is used as a mixture of potions proven to decrease creatinine significantly. From the 11 kinds of plants, only known 5 plants that potentially improve kidney function seen from its ability to reduce levels of uric acid, creatinine, and serum ureum 5 crops such as *S. crispus, O. stamieus, C. arabica, C. xanthorriza*, and *C. domestica.*

Histopathological examination of kidney

The results of the renal histopathologic study (Fig. 1) of all treatments showed the presence of necrotic focal damage in the tubule epithelium. The cause is due to acute cell damage or trauma such as lack of oxygen, extreme temperature changes, increased excessive antioxidant levels, and mechanical injury. These cell deaths occur uncontrollably which can cause cell damage or an inflammatory response. Damage on kidney organ will interfere with most kidney function. The kidneys play an important role in the release of toxic substances or toxins, maintaining of fluid balance, maintaining a balance of acid and alkaline levels from body fluids, maintaining the balance of salts and other substances in the body, so in this case the kidneys play a role in the release of substances the ingredients contained in the herbal concoction consumed by rats.In addition, materials that have activities such as sulfonamide antibiotics and nonsteroidal anti-inflammatory drugs such as diuretics can damage tubule epithelial cells. The ingredients that have diuretic effects in renal failure include *S. crispus* [21], *O. stamineus* [20], *S. officinarum* [12], and *C. domestica* [22].

Kidney damage can be exacerbated by precipitation of calcium oxalate crystals in the kidney tubules. Excessive oxalate intake is known to come from *A. bilimbi*. The star fruit is very acidic and is usually used for traditional therapies of hyperlipidemia, hypertension, and diabetes [23]. However, from its use, there are side effects on the kidney and nervous system [24]. Oxalic acid in star fruit has direct toxic effects on renal tubules and renal interstitium. Facilitate the formation of oxalic crystals by endocytosis by renal epithelial cells and increases the incidence of proliferative responses. These crystals also stimulate specific genes in renal tubular cells, including connective tissue, and growth factor genes that lead to interstitial fibrosis. All patients who have a history of consuming star fruit juice have calcium oxalate crystals in their urine. Moreover, patients undergoing biopsy have polarized intracellular oxalate crystals [25].

Immunohistochemistry of renal organs

The result of nuclear factor kappa B (NF-κB) expression (Fig. 2) did not show any significant difference from each test group. Of the 11 kinds of mixed plants from the herbs known coffee has kahweol compounds that are able to inhibit TNF-α expression induced through the NF-κB activation pathway. In general, kahweol is an anti-inflammatory and anti-atherosclerotic agent by affecting the expression and interaction of molecular adhesion on endothelial cells [26]. The activation of the NF-κB pathway generally underlies the inflammatory process and improved translocation of NF-κB. Leukocytes from diabetes patients by AGEs or ROS are oxidative stress. Increased levels of glucose are known to produce ROS in mesangial cells, which play a role in macrophage infiltration of renal failure and activate the NF-κB pathway. The NF-kB pathway plays a role in macrophage infiltration of gene expression, and inflammation of the kidney due to hyperglycemia [27].

The results of COX-2 expression (Fig. 3) and TGF-β expression (Fig. 4) showed no significant differences from each test group. Of the 11 kinds of plant mixture of the kidney failure herb known kinir, white turmeric, and temulawak contain kurkumin. According to Khajehdehi curcumin is able to inhibit cytokines and the production of TGF-β from various

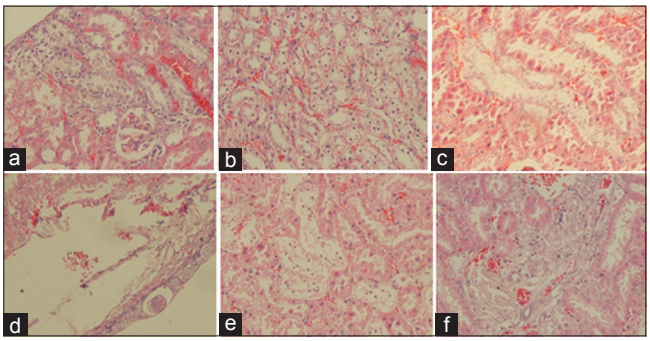

Fig. 1: Histopathological images of renal tissue sections of normal group (a), negative group (b), positive group (c), dose 18 ml/kg body weight (BW) (d), dose 36 ml/kg BW (e), dose 54 ml/kg BW (f)

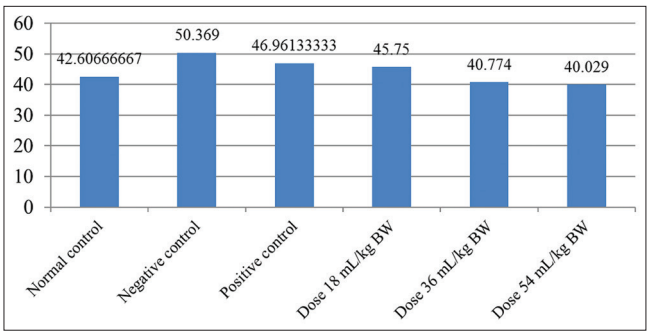

Fig. 2: The result of nuclear factor kappa B parameters measurement

factors involved in chronic kidney disease and primary and secondary glomerulonephritis pathogenesis [28].

Rosmarinic acid is a phenolic compound and one of the components of the extraction on the *O. stamineus* [29]. The results of research were conducted by Domitovic *et al.* in cisplatin-induced mice, rosmarinic acid function as nephroprotective [30]. In other plants such as ginger, white turmeric and turmeric contain curcumin compounds capable of inhibiting NF-κB activation in the kidney in NRK-52E epithelial cells *in vitro* and have been shown to decrease NF-κB expression in kidney organs in diabetic mice [31]. Curcumin activity prevents the occurrence of diabetic nephropathy by inhibiting oxidative stress due to hyperglycemia that is able to activate the NF-κB pathway. With the inhibition of the NF-κB pathway, TGF-β, ET-1, and eNOS are not expressed in the mesangial cells [32].

CONCLUSION

Measurement of blood biochemical parameters showed significant increase of BUN levels in all dose variation groups after being given herbs, compared to the negative control group. The result of the examination of biochemical parameters of creatinine levels statistic showed significant ($p<0.05$) decrease in the dose 18 and 36 mL/kg BW compare with the negative group. Serum uric acid was not significantly different between hyperglycemic and healthy control groups. Study on histopathology kidney organs there are damages to each test in each organ that is necrosis. Expressions of NF-κB, COX-2, and TGF-β showed no significant differences from each of the test dose groups compared with negative controls. Need more research to know that activity as nephroprotective.

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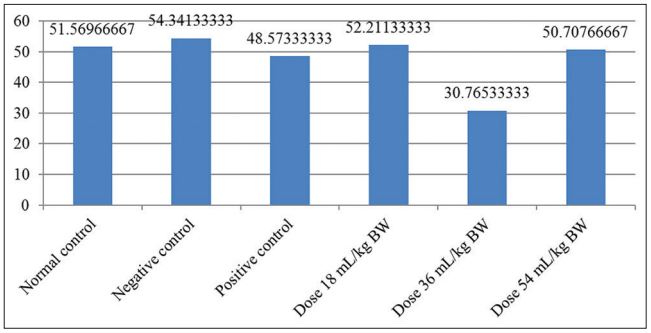

Fig. 3: The result of cyclooxygenase-2 parameters measurement

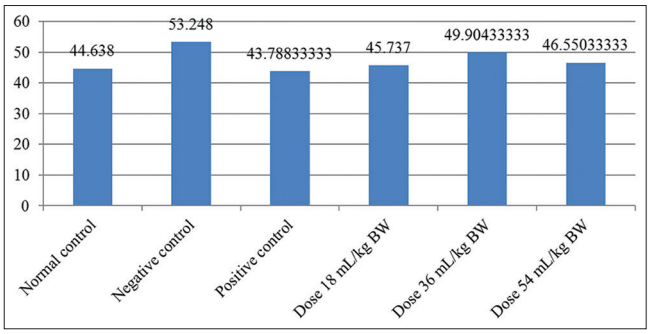

Fig. 4: The result of transforming growth factor-beta parameters measurement

AUTHOR'S CONTRIBUTIONS

The authors thank The Indonesian Health Ministry for the financial support and the management of Sardjito Hospital for their help with examination of histopathology organ. This study was designed and coordinated by Kintoko, Sitarina Widyarini, and Hardi Astuti Witasari as the principal investigators provided conceptual and technical guidance for all aspects of the project. Nurkhasanah developed the theoretical framework. Slamet Wahyono supervised the project. Djati Wulan Kusumo, Halid Kapri, Tya Muldiyana, Hasni Pulhehe, Yuli Nurullaili Efendi, Tri Puspita Yuliana and Urmatul Waznah performed the experiment, analyzed data, and wrote the manuscript.

CONFLICTS OF INTEREST

The authors do not have any conflicts of interest to declare.

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