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The Effect of Dandang Gendis Extract (*Clinacanthus nutans*) on Kidney Histopathological Features of Diabetic Rats Model

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ABSTRACT

Changes in kidney homeostasis due to diabetes can cause oxidative stress which then caused tissue damage that leads to diabetic nephropathy. *Clinacanthus nutans* extract is known to contain antioxidants that are reported to play an important role in the body's defense system against oxidative stress to minimize tissue damage. This study aims to know the effect of *Clinacanthus nutans* leaf extract administration on kidney histopathological features of the diabetic rats model. A total of 35 rats were induced by streptozotocin which then divided into 5 groups and given *Clinacanthus nutans* extract with a dose of 75 mg/kgBW, 150 mg/kgBW and 300 mg/kgBW then compare with CMC-Na as control and metformin as standard drug for 14 days. The kidney histopathology was evaluated under a light microscope against the damage criteria that occurred in the proximal tubules of the kidney. As a result the least amount of kidney damage was on treatment group at dose 300 mg/kgBW, followed by extract with dose 75 mg/kgBW, 150 mg/kgBW, and metformin. In conclusion *Clinacanthus nutans* extract with a dose of 75 mg/kgBW, 150 mg/kgBW, and 300 mg/kgBW can improve the kidney histopathological feature of the diabetic rats model.

Keywords: diabetes mellitus; histopathology; diabetic nephropathy; *Clinacanthus nutans*

INTRODUCTION

There are approximately 10.3 million adults aged 6-79 years with diabetes in Indonesia which makes Indonesia the sixth highest in the world in 2017 and in 2045 it is estimated that the number of diabetics in Indonesia will reach 16.7 million people⁽¹⁾. Complications that most affect patients with diabetes mellitus are abnormalities of the blood vessel system as a result of metabolic complications. Kidney is an organ that is rich in micro vascularization and is sensitive to changes in hemodynamic and metabolic conditions, which makes it a vulnerable target for changes in the microenvironment⁽²⁾. Data collected from 54 countries reveal that more than 80% cases of end-stage kidney disease are caused by diabetes, hypertension, or a combination of both. The prevalence of end-stage kidney disease is 10 times higher in people with diabetes compared with those who don't⁽³⁾.

Diabetes mellitus (DM) is a metabolic disease with symptoms of hyperglycemia as a result of lack of insulin production due to pancreatic beta cell dysfunction, increased cellular resistance to insulin, or both⁽⁴⁾. If blood sugar levels in diabetes mellitus are not maintained, complications can occur, one of them is diabetic nephropathy, which is a condition in which there are changes in kidney structure due to excessive blood sugar. Because of the hemodynamic and metabolic imbalances, kidney will undergo structural changes that result in progressive disruption of kidney function. Kidney disease due to diabetes (diabetic nephropathy) is one of the leading causes of terminal kidney failure and the highest death among other complications of diabetes mellitus⁽²⁾. Reactive oxygen species (ROS) play an important role in the pathogenesis of diabetes complications because, in persistent hyperglycemia, ROS production is increased. An increase in excessive ROS production and a weak antioxidant defense system support an increase in oxidative stress⁽⁵⁾. Oxidative stress can cause the oxidation of important macromolecules including proteins, lipids, carbohydrates, and DNA. This important macromolecular oxidation will also cause tissue damage⁽⁶⁾. Antioxidants are believed to play an important role in the body's defense system against ROS so as to minimize tissue damage⁽⁷⁾.

Clinacanthus nutans Lindau which is commonly known as dandang gendis or 'snake grass' is one of the important species of the family Acanthaceae. *Clinacanthus nutans*, which has been used as a herbal medicine in Malaysia, Indonesia, Thailand, and China, is believed to have various potentials treating various disease including skin rashes, insect and snake bites, lesions due to herpes simplex virus, gout, and diabetes⁽⁸⁾. Ethanol extract of

Clinacanthus nutans is reported to have anti-diabetic properties and has been tested to contain antioxidants such as flavonoids, saponins, and tannins⁽⁹⁾.

Flavonoids can modulate carbohydrate and fat metabolism, reduce hyperglycemia, dyslipidemia and insulin resistant, increase adipose tissue metabolism, and reduce oxidative stress and signaling pathways that are sensitive to stress and inflammatory processes, reduce apoptosis, and increase proliferation of pancreatic β cells^(10,11). *Clinacanthus nutans* cultivation is fairly easy because it is enough to spread the seeds to moist soil, dry them, or cut the stems⁽¹²⁾. That means *Clinacanthus nutans* is easily cultivated and economical enough for alternative diabetes therapies. Based on the reasons above, authors are interested in conducting research on the effect of ethanolic extract of *Clinacanthus nutans* on the histopathological features of diabetic rats model.

METHODS

This study was an experimental research with a complete randomized design. A total of 35 male white rats (*Rattus norvegicus*) Wistar strains were being used. These rats then induced by streptozotocin (STZ) and then given a treatment in the form of extracts of *Clinacanthus nutans* with a dose of 75 mg/kgBW, 150 mg/kgBW, and 300 mg/kgBW, 1000 mg/x metformin, and untreated control (Only with CMC-Na). The parameter we measured was a histopathological feature of the diabetic model *Rattus norvegicus* Wistar strain's kidney

Total of 35 rats were induced by streptozotocin 50 mg/kgBW which was then after 2 days after induction if random blood sugar was measured above 200 mg/dl, rats were divided into 5 groups and given *Clinacanthus nutans* leaf extract according to the dose i.e K1 (75 mg/kgBW), K2 (150 mg/kgBW), and K3 (300 mg/kgBW) then compare with K0 (CMC-Na as a control) and K4 (metformin 1000 mg/kgBW as a standard drug). After 15 days, the rats were terminated with ether and the kidneys were harvested and fixed in 10% formalin for 24 hours and then blocked in paraffin.

After blocked in paraffin, slices (2-micron thickness) were stained with Hematoxylin-Eosin using standard protocols. The examination was carried with the reversible and irreversible damage criteria that occurred in the epithelial cells of proximal tubules of the kidneys. The irreversible damage in question is necrosis, characterized by loss of the nucleus, cell fragmentation, and release of cytoplasmic contents. The reversible damage in question is surface blebs, increased eosinophilic density in the cytoplasm, and cell swelling⁽¹³⁾. At least 5 images were randomly captured with Olympus CX23 light microscope at 200x magnification using cellSens software (ver.2.3, Olympus Corporation, Shinjuku, Tokyo, Japan). The reversible and the irreversible cells were counted manually with the help of Cell Counter in ImageJ software ver.1.52a.

The data analysis was performed by a non-parametric test in SPSS software ver.16.00. The median and interquartile range were used as descriptive statistics. Because according to the Shapiro-Wilk test the variables were found not to be normally distributed among groups, Kruskal-Wallis and Mann-Whitney were used to make pairwise comparisons.

RESULTS

Table 1. Mean and standard deviation of kidney damage percentage

Group	n	Mean	Standard Deviation
K0	7	63%	8%
K1	6	21%	4%
K2	7	29%	9%
K3	5	19%	4%
K4	5	37%	16%

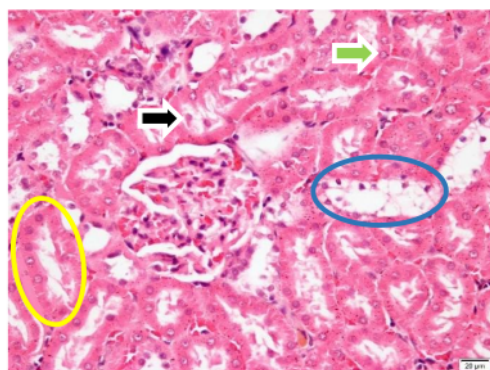


Figure 1. Histopathological features of *Rattus norvegicus* kidney with STZ induction and treatment with *C. nutans* dose 300 mg/kgBW. Black arrow = irreversible damage/necrosis, Green Arrow = reversible damage/degeneration. Yellow circle = proximal tubule. Green circle = distal tubule (HE, 400x).

The results of histopathological examinations on the kidney tissues are shown in Table 1. As can be seen, the group with the least amount of proximal tubule's epithelial cell damage was the group with the administration of *Clinacanthus nutans* extract at a dose of 300 mg/kgBW followed by the group with a dose of 75 mg/kgBW, 150 mg/kgBW, and the metformin group. The control group had the most damage. For the dose of 300 mg/kgBW and 75 mg/kgBW there was no significant difference ($p > 0.05$), but, there's a significant difference between treatment group 300 mg/kgBW and 150 mg/kgBW and between 150 mg/kgBW and 75 mg/kgBW. However, The treatment group with a dose of 300 mg/kgBW, 150 mg/kgBW, 75 mg/kgBW shows a significant difference with metformin and control group ($p < 0.05$). The control group had the most damage.

DISCUSSION

Rats were induced with streptozotocin (STZ) to make a diabetes mellitus model. Streptozotocin affect glucose oxidation and decrease insulin biosynthesis and secretion⁽¹⁴⁾. Through the GLUT2 glucose transporter, STZ enters the pancreatic β cells causing decreased expression of GLUT2 which results in increased insulin resistance and increased blood glucose levels due to decreased sensitivity of peripheral insulin receptors⁽¹⁵⁾. Diabetic nephropathy is a microvascular complication of diabetes mellitus. Clinically microalbuminuria is an early biomarker of diabetic nephropathy, but recent findings indicate that the proximal tubule has an important link in the development of diabetic nephropathy and is an alternative clinical approach for early detection of kidney disease due to diabetes⁽¹⁶⁾.

In diabetic nephropathy the proximal tubules undergo various structural changes such as tubular atrophy, interstitial fibrosis and peritubular capillary rarefaction, each of which is closely related to decreased kidney function. Because of their high energy requirements and dependence on aerobic metabolism, proximal tubules are prone to ischemic injury in diabetes as a consequence of increased consumption. This pathophysiological disorder joins a non-ischemic mechanism to induce apoptosis and fibrosis in the nephron which simultaneously causes chronic loss of function and a tendency for acute renal failure. Diabetes-induced injury to the proximal tubules also leads to the pathology of glomerular diabetic nephropathy and postglomerular hypoperfusion, whereas interstitial fibrotic expansion suppresses and subsequently disrupts the local microvascular system namely the renin-angiotensin system⁽¹⁷⁾.

The percentage of renal proximal tubular cell damage in the control group that induced with streptozotocin without therapy had the most amount. This shows that in STZ induced diabetic rats there is kidney damage and if given diabetes therapy will improve. Oxidative stress plays an important role in the progression and development of diabetes and its complications⁽¹⁸⁾. Various clinical studies and experimental models show that in diabetes mellitus cell damage occurs, involve apoptosis and autophagy as a result of oxidative stress and the release of ROS⁽¹⁹⁾. On the histopathological features of the kidney can be found reversible damage (Surface blebs, increased eosinophilic density in the cytoplasm, and swelling of cells) and irreversible damage (necrosis, characterized by loss of the nucleus, cell fragmentation, and release of cytoplasmic contents) in the proximal tubules of the kidney⁽¹³⁾.

Clinacanthus nutans leaf ethanolic extract has potential as an antidiabetic, antioxidant, and anti-inflammatory⁽²⁰⁾. In previous studies, administration of *Clinacanthus nutans* extract to diabetes mellitus rats model can reduce blood sugar levels⁽²¹⁾. In a study conducted by Khoo (2018) the active compounds of flavonoids, especially flavones, were found in ethanolic extracts of leaves of cormorant leaves. Same goes for research conducted by Chelyn *et al.* (2014) showed that c-glycoside flavones such as shaftoside, orientin, orientin, isovitexin, and vitexin make up the majority of the flavonoid classes found. The main mechanism in the antidiabetic activity of c-glycoside flavonoids is the inhibition of the formation of AGE, α -glucosidase, aldose reductase, and protein tyrosine phosphatase; stimulates glycogen storage and activation of insulin signaling⁽²²⁾. Flavonoids can also play a role as radical scavengers because free radicals play an important role in the pathogenesis of inflammation in the process of kidney damage⁽²³⁾. The flavonoid content can further inhibit oxidative stress which has an effect on delaying cell damage in tissues including pancreatic β cells and renal tubular cells^(20,24,25).

The results of this study indicate that the group given *Clinacanthus nutans* extract 300 mg/kgBW had the smallest percentage of kidney damage than the other groups. However, these results after being tested with the Mann-Whitney test were not significantly different from the groups given 75 mg/kgBW of *Clinacanthus nutans* extract. Those two groups after being tested with a group given 150 mg/kgBW extract there was a significant difference in between this can be called the non-monotonic dose response, but the treatment group which was given *Clinacanthus nutans* extract with dose of 75 mg/kgBW, 150 mg/kgBW, and 300 mg/kgBW has a significantly less amount of damage compared to the control group and the group that was only given metformin 1000 mg. The occurrence of dose response with an insignificant increase indicates a non-monotonic dose response relationship. Non-monotonic dose response relationship if formed into a curve it will form the letter U or inverted letter U. The mechanism for the occurrence of a non-monotonic dose response is caused by various theories, including cytotoxicity and dose-dependent modulation metabolism⁽²⁶⁾. However, this study cannot yet explain which mechanism that makes the dose response not linear. However this proves that the administration of *Clinacanthus nutans* leaf extract can improve the kidney histopathological features of diabetic rats model because there is a significant reduction in the percentage of kidney damage in rats that have been induced by STZ.

CONCLUSION

Clinacanthus nutans leaf ethanolic extract with a dose of 75 mg/kgBW, 150 mg/kgBW, and 300 mg/kgBW can improve kidney histopathological feature of the diabetic rats model.

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