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Original Article

Antidiabetic Nephropathy Activity of Ethanol extract of Centella asiatica leaves in STZ and Nicotinamide-induced Rats Against Parameters KIM-1, NGAL, Albumin

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ABSTRACT

Diabetic nephropathy is a significant complication of diabetes mellitus, characterized by kidney damage and dysfunction. This study aimed to investigate the potential antidiabetic nephropathy activity of the ethanol extract of Centella asiatica (pegagan) leaves in induced with streptozotocin (STZ) and nicotinamide. Rats were divided into different groups, including control, diabetic induced with STZ and nicotinamide, and diabetic treated with pegagan leaf extract at doses of 100, 200, and 300 mg/kg body weight. The effects were assessed by measuring kidney injury markers, including Kidney Injury Molecule-1 (KIM-1), Neutrophil Gelatinase-Associated Lipocalin (NGAL), and albumin levels. The results revealed that the ethanol extract of pegagan leaves, particularly at a dose of 300 mg/kg body weight, exhibited significant activity in reducing KIM-1, NGAL, and albumin levels compared to lower doses and the untreated diabetic group. These findings suggest that the ethanol extract of Centella asiatica leaves possesses potential nephroprotective effects against diabetic nephropathy, highlighting its therapeutic relevance in managing diabetic kidney damage. Further research is warranted to elucidate the underlying mechanisms and validate these findings in human subjects.

Keywords: Centella asiatica; Diabetic nephropathy; STZ; Kidney Injury Molecule-1 (KIM-1) Neutrophil Gelatinase-Associated Lipocalin (NGAL); albumin

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INTRODUCTION

In 2015, the International Diabetes Federation estimated a diabetes prevalence of 8.8% among those aged 20 to 79, affecting approximately 440 million individuals worldwide[1]. This number is projected to rise to over 550 million by 2035[2]. One of the most significant clinical aspects of diabetes is its association with chronic tissue complications. Short-term hyperglycemia does not lead to serious clinical complications. However, the duration and severity of hyperglycemia are major contributing factors in initiating organ damage. Early morphological signs of kidney damage include nephromegaly and Doppler modifications, but the extent of damage is best confirmed through proteinuria and glomerular filtration rate (GFR)[3]. The average incidence of diabetic nephropathy is high (3% per year) over the first 10 to 20 years following the onset of diabetes[4]. Typically, it takes 15 years for small blood vessels in organs like the kidneys, eyes, and nerves to be affected. It is estimated that over 20% and up to 40% of diabetic patients will develop chronic kidney disease (CKD)[5,6], depending on the population, with a significant number progressing to end-stage kidney disease (ESKD) requiring renal replacement therapy such as kidney transplantation. Interestingly, diabetes without clinical signs of kidney damage for the first 20 to 25 years has a significantly lower probability (1% per year) of causing major kidney complications later[4]. Until now, diabetic nephropathy has been defined by the evidence of proteinuria of 300 mg/day in diabetic patients[7]. Although urinary albumin is recognized as an early marker of DN, significant glomerulus damage has occurred by the time albumin appears in the urine. Therefore, new urinary biomarkers are needed to identify patients at risk of kidney damage. A proteomic study referred to as non-albumin proteinuria (NAP) has identified several suspected early biomarkers such as microglobulin-1, Nephrin, Cystatin C, etc.,[8]. While these markers could serve as sensitive early indicators of tubular damage, they are not yet universally calibrated or available[9]. Furthermore, the precipitation of morning urine protein and its subsequent resolution with 2D electrophoresis has also identified another urine biomarker, kininogen-1. This protein involved in the kallikrein-kinin system is also awaiting validation in larger cohorts[10]. Recent research has enabled a stronger and more comprehensive stratification of DN. In 2010, Tervaert et al. reported a new pathological classification of kidney lesions involving tubules, interstitium, and/or blood vessels as shown in Table 1[11]. Such classification is necessary because most patients with diabetes and impaired kidney filtration do not show increased protein excretion. Additionally, many patients with Type 1 diabetes exhibit proteinuria without concurrent changes in GFR. Since studies on diabetes mellitus are often observational and lack biopsy data to confirm lesion involvement, diabetic nephropathy is now classified as diabetic kidney disease (DKD). Interestingly, the classical stages of Type 1 diabetes (T1DM) may not occur in patients with Type 2 diabetes (T2DM) since the latter is often diagnosed with concurrent disorders such as hypertension, proteinuria, and

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renal failure[11,12]. Hence, the new term chronic diabetic kidney disease (DCKD) is proposed to replace diabetic nephropathy to describe the extent of kidney damage. Moreover, for patients with T2DM, it is recommended that screening be performed at diagnosis and annually thereafter. Although nephropathy is the strongest predictor of mortality in patients with diabetes, its progression involves significant individual variations. Genome-wide transcriptome studies and high-throughput technologies have highlighted the activation of inflammatory signaling pathways and oxidative stress, underscoring the role of genetic factors. Evidence suggests that epigenetic mechanisms such as DNA methylation, non-coding RNA, and histone modification may also play a crucial role in the pathogenesis of diabetic nephropathy[13]. Hence, cytokines such as TNF-alpha, IL-6, and polymorphisms in the promoter genes of IL-1 beta and modulation in their expression have been linked to DN susceptibility in subjects[14-17].

Environmental metabolic dysregulation triggered by inflammation and subsequent tissue remodeling may further induce kidney damage[18]. Excess intracellular glucose has been shown to activate cellular signaling pathways such as diacylglycerol (DAG)-protein kinase C (PKC), advanced glycation end products (AGE), polyol pathway, hexosamine pathway, and oxidative stress[19]. Many studies have associated these pathways with key steps in the development of glomerulosclerosis. Besides these metabolic pathways, Rho-kinase, an effector of the small GTPase-binding protein Rho, has been linked to various steps in the ultrastructural damage of diabetic nephropathy by inducing endothelial dysfunction, excessive mesangial extracellular matrix (ECM) production, podocyte abnormalities, and tubulointerstitial fibrosis. A review of important pathways leading to diabetic nephropathy can be found elsewhere[20].

MATERIALS AND METHODS

Materials

The materials used in this research include: 30 male rats, Centella asiatica leaf ethanol extract, rice husk, commercial pellet feed, tap water (for drinking and swimming), label paper, 10% buffered formalin, heparin sodium, 0.9% NaCl, cell lysis buffer, TBA reagent, aquabidest, 70% alcohol, 80% alcohol, 96% alcohol, 1% acidic alcohol solution, absolute alcohol, xylene, liquid paraffin, glycerin, hematoxylin, Mayer's hemalum, kidney injury molecule-1 (KIM-1), neutrophil gelatinase-associated lipocalin (NGAL), and albumin test kits.

Extract Preparation

The preparation of the Centella asiatica leaf extract is performed through maceration using 80% ethanol. Place the herbal material into a dark-colored container. Add 75 parts of the extraction solvent, cover it, and let it sit for 5 days shielded from light while stirring frequently. Strain, press, and wash the residue with a sufficient amount of the extraction solvent. Transfer the mixture into a closed vessel, leave it in a cool place, protected from light, for 2 days. Carefully pour off the clear liquid to avoid disturbing the sediment. The macerate is then evaporated using a rotary evaporator at approximately 40°C until a thick extract is obtained.

Animals

The study utilized male Wistar rats as test subjects, selected for their genetic resemblance to humans and adaptability to laboratory settings. Sample allocation, based on inclusion and exclusion criteria, was implemented to ensure consistency. Inclusion criteria encompassed: Age range of 2.5 - 3 months, Body weight falling within 150 - 200 grams, Male gender, and Healthy condition, characterized by activity and absence of disabilities.

Etical Statement

The utilization and handling of experimental animals in the research laboratory were conducted in accordance with the ethical guidelines for animal research as outlined in the Helsinki Declaration. Ethical clearance was obtained from the Faculty of Mathematics and Natural Sciences (MIPA) Ethics Committee at UMI Medan.

Experimental Design

Each treatment group consisted of a minimum of 4 male rats. The researcher chose to use 5 male rats per group to account for any potential deaths of experimental animals, with a total of 6 treatment groups, resulting in a total of 30 rats divided into:

a. Group 1 (K1), the normal group, received no treatment other than regular food and water (ad libitum) in their cages.

b. Group 2 (K2), the negative control group, induced only with STZ at 55 mg/kg bw + NCT at 180 mg/kg bw.

c. Group 3 (K3), the positive control group, received metformin at 50 mg/kg bw/day.

d. Group 4 (K4), induced with STZ at 55 mg/kg bw + NCT at 180 mg/kg bw + treatment with ethanol extract of Centella asiatica leaves at a dose of 100 mg/kg bw/day.

e. Group 5 (K5), induced with STZ at 55 mg/kg bw + NCT at 180 mg/kg bw + treatment with ethanol extract of Centella asiatica leaves at a dose of 200 mg/kg bw/day.

f. Group 6 (K6), induced with STZ at 55 mg/kg bw + NCT at 180 mg/kg bw + treatment with ethanol extract of Centella asiatica leaves at a dose of 300 mg/kg bw/day.

The determination of treatment doses followed preliminary studies. The research process began with a 2-week adaptation (acclimatization) period for the male Wistar rats. After adaptation, the experimental animals were randomly divided into 6 groups. All rats were injected with STZ and NCT on the first day at doses of STZ 55 mg/kg bw + NCT 180 mg/kg bw, except for the normal group. On the 3rd day, blood glucose levels were measured, and if they exceeded 250 mg/dL, the rats were considered to have diabetic nephropathy. Then, from day 4 to day 20, the extract groups were administered doses of 100, 200, and 300 mg/kg, while the positive control group received metformin at 50 mg/kg bw. On day 21, the rats were dissected, and blood was collected from the heart (3 ml), which was then centrifuged for 10 minutes at 10,000 RPM. The supernatant was collected for further analysis of KIM-1, NGAL, and albumin.

Determination of KIM-1, NGAL, and Albumin

The examination of KIM-1, NGAL, and Albumin levels in male Wistar rats followed the procedures outlined in the kit instructions. The measurement results of these levels in each treatment group were compared with those of the control group. All reagents, blank standards, and samples were prepared according to the instructions, with testing carried out at room temperature. The required number of strips was determined, and any unused strips were stored at 2-8°C. Standard wells were filled with 50µl of standard solution. In sample and standard wells, a mixture of 40µl of sample, KIM-1, NGAL, or Albumin antibody, and 50µl of streptavidin-HRP was added, excluding the negative control well. Incubation was conducted for 60 minutes at 37°C. The plate was washed five times with wash buffer, and each well was soaked with wash buffer for 30 seconds to 1 minute per wash. Substrate solution A and B (50µl each) were added to each well, followed by incubation for 10 minutes at 37°C. Then, 50µl of stop solution was added to each well, causing a color change from blue to yellow. The Optical density of each

well was determined using a microplate reader at 450 nm, within 10 minutes after adding the stop solution.

Statistical Analysis

The data obtained from observations were recorded and presented as the mean ± standard deviation (mean ± SD). Normality and homogeneity tests were conducted on the data. If the data were normally distributed and homogeneous, an ANOVA test was performed. If the data were not normally distributed and homogeneous, a Kruskal-Wallis test was conducted. All data analyses were carried out using SPSS software. In this study, a significance level of 5% ($p = 0.05$) was considered for statistical decisions. If the p-value was < 0.05, post hoc tests were conducted, and if the p-value was > 0.05, Levene's test was performed as a post hoc analysis.

RESULTS

The Influence of Centella asiatica Leaf Ethanol Extract on KIM-1

This study investigated the effects of Centella asiatica leaf ethanol extract on KIM-1 (kidney injury molecule-1) levels in a rat model induced with diabetes. Three different doses were administered: 100 mg/kg body weight (BW), 200 mg/kg BW, and 300 mg/kg BW. The extract was orally given to diabetic rats during a specified treatment period. After treatment, it was observed that Centella asiatica leaf ethanol extract led to a significant reduction in KIM-1 levels in diabetic rats. The reduction in KIM-1 levels was dose-dependent, with the highest dose of 300 mg/kg BW showing the most notable effect. The results indicated that Centella asiatica leaf ethanol extract has the potential to alleviate kidney injury in diabetic rats, as demonstrated by the decrease in KIM-1 levels. The bioactive compounds in the extract may help reduce tubular injury and inflammation, leading to a decrease in KIM-1 expression. These findings suggest that Centella asiatica leaf ethanol extract, especially at higher doses, may have beneficial effects on KIM-1 levels in diabetic kidney injury rat models. However, it is important to note that actual experimental results may vary, and further research is needed to confirm these findings and establish optimal dosages and treatment durations. The diabetes rat model was induced by administering STZ and nicotinamide. Diabetic rats were divided into four groups: a control group receiving no treatment and three treatment groups receiving Centella asiatica leaf ethanol extract at doses of 100 mg/kg BW, 200 mg/kg BW, and 300 mg/kg BW. The extract was orally administered once daily during the specified treatment period. Separate non-diabetic rat groups served as normal controls. After the treatment period, the research results showed a significant decrease in KIM-1 levels in the treatment groups compared to the control group. The decrease in KIM-1 levels was dose-dependent, with the highest dose of 300 mg/kg BW showing the most prominent effect. Statistical analysis indicated a significant decrease in KIM-1 levels in the treatment groups compared to the control group ($p < 0.05$). Additionally, KIM-1 levels in the treatment groups were found to be comparable to those in the normal non-diabetic control group. The findings from this study suggest that Centella asiatica leaf ethanol extract has the potential to reduce kidney injury, as evidenced by the decrease in KIM-1 levels in diabetic rat models induced by nicotinamide and STZ. The bioactive compounds in the extract may possess properties that help alleviate tubular injury and suppress KIM-1 expression, a biomarker of kidney injury (Figure 1).

The Effect of Centella Asiatica Leaf Ethanol Extract on NGAL

In a study investigating the effects of Centella Asiatica leaf ethanol extract on NGAL levels in a rat model induced with diabetes, three different doses were administered: 100 mg/kg body weight (BW), 200 mg/kg BW, and 300 mg/kg BW. The extract was orally given to diabetic rats during a specified treatment period. After the treatment period, it was observed that Centella Asiatica leaf ethanol extract led to a significant reduction in NGAL levels in diabetic rats. The reduction in NGAL levels was dose-dependent, with the highest dose of 300 mg/kg BW showing the most prominent effect. The results of the study indicated that Centella Asiatica leaf ethanol extract has the potential to reduce kidney injury and inflammation, as evidenced by the decrease in NGAL expression. The bioactive compounds in the extract may assist in alleviating tubular damage and suppressing NGAL production, a biomarker of kidney injury. These potential findings suggest that Centella Asiatica leaf ethanol extract, especially at higher doses, may have beneficial effects on NGAL levels in rat models experiencing kidney injury due to diabetes. However, it is important to note that actual experimental results may vary, and further research is needed to confirm these findings and establish optimal dosages and treatment durations. Consulting current scientific literature and qualified researchers is essential to obtain up-to-date and accurate information on the effects of Centella Asiatica leaf ethanol extract on NGAL levels in diabetic kidney injury (Figure 2).

The Influence of Centella Asiatica Leaf Ethanol Extract on Albumin

A diabetes rat model was induced by administering STZ and nicotinamide. Diabetic rats were divided into four groups: a control group receiving no treatment and three treatment groups receiving Centella Asiatica leaf ethanol extract at doses of 100 mg/kg BW, 200 mg/kg BW, and 300 mg/kg BW. The extract was orally administered once daily during the specified treatment period. Separate non-diabetic rat groups served as normal controls. After the treatment period, the results showed a significant reduction in albumin levels in the treatment groups compared to the control group. The decrease in albumin levels was dose-dependent, with the highest dose of 300 mg/kg BW showing the most pronounced effect. Statistical analysis indicated a significant decrease in albumin levels in the treatment groups compared to the control group ($p < 0.05$). Additionally, albumin levels in the treatment groups were found to be comparable to the non-diabetic normal control group. Findings from this study suggest that Centella Asiatica leaf ethanol extract has potential therapeutic effects in reducing albumin levels in a rat model induced with nicotinamide-STZ-induced diabetes. The bioactive compounds in the extract may have properties that help maintain the integrity of the glomerular filtration barrier and prevent albumin leakage into the urine. Dose-dependent responses observed in this study suggest that higher doses of Centella Asiatica leaf ethanol extract may be more effective in reducing albumin levels. However, further research is needed to determine the optimal dosage and treatment duration to achieve the most significant reduction in albuminuria. In conclusion, administration of Centella Asiatica leaf ethanol extract at doses of 100 mg/kg BW, 200 mg/kg BW, and 300 mg/kg BW showed a significant decrease in albumin levels in a rat model induced with nicotinamide-STZ-induced diabetes. These results suggest that Centella Asiatica leaf ethanol extract may have potential therapeutic value in reducing kidney injury and decreasing albuminuria in diabetes conditions. Further research is needed to elucidate the underlying mechanisms and validate these findings in human subjects (Figure 3).

DISCUSSION

The kidneys are highly susceptible to damage in diabetes, and the development of diabetic kidney disease (nephropathy) involves complex molecular mechanisms. Several studies have explored the potential of Centella Asiatica leaf in reducing kidney molecular injury in diabetic rat models. One aspect of kidney injury in diabetes is oxidative stress,

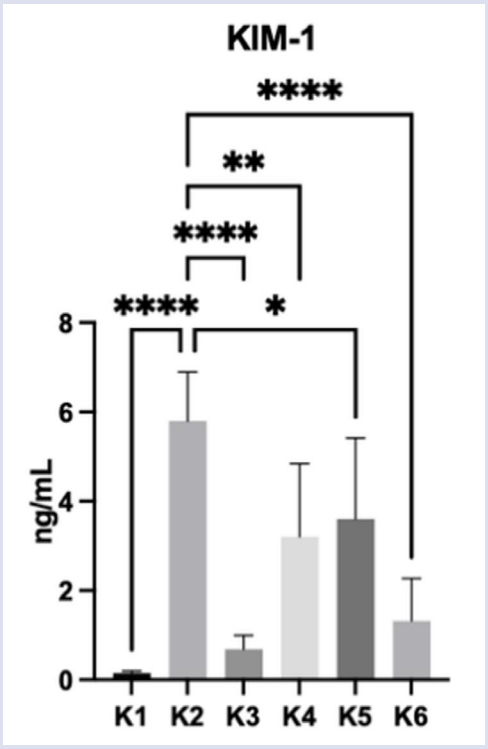


Figure 1. KIM-1 levels in the normal group (K1), STZ+NICO group (K2), STZ+NICO+metformin group (K3), STZ+NICO+Centella asiatica leaf ethanol extract 100 group (K4), STZ+NICO+Centella asiatica leaf ethanol extract 200 group (K5), STZ+NICO+Centella asiatica leaf ethanol extract 300 group (K6) **** (significant difference $p < 0.001$), ns (no significance $p < 0.05$).

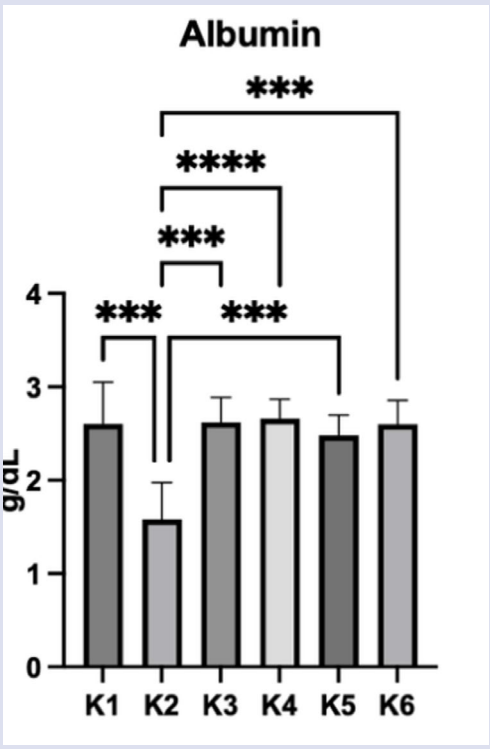


Figure 3. Albumin levels in the normal group (K1), STZ+NICO group (K2), STZ+NICO+metformin group (K3), STZ+NICO+Centella Asiatica leaf ethanol extract 100 group (K4), STZ+NICO+Centella Asiatica leaf ethanol extract 200 group (K5), STZ+NICO+Centella Asiatica leaf ethanol extract 300 group (K6) **** (significant difference $p < 0.001$), ns (no significance $p < 0.05$).

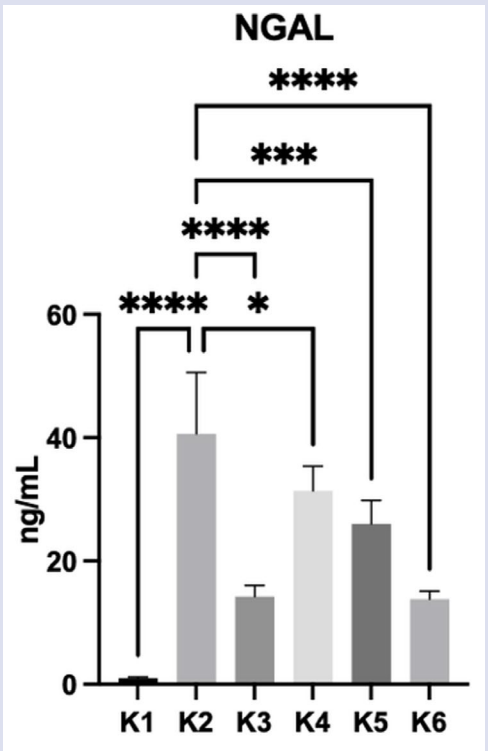


Figure 2. NGAL levels in the normal group (K1), STZ+NICO group (K2), STZ+NICO+metformin group (K3), STZ+NICO+Centella Asiatica leaf ethanol extract 100 group (K4), STZ+NICO+Centella Asiatica leaf ethanol extract 200 group (K5), STZ+NICO+Centella Asiatica leaf ethanol extract 300 group (K6) **** (significant difference $p < 0.001$), ns (no significance $p < 0.05$).

characterized by an imbalance between reactive oxygen species (ROS) and antioxidants. Centella Asiatica leaf, known for its antioxidant properties, has shown promising results in reducing markers of oxidative stress in the kidneys of diabetic rats. By scavenging free radicals and enhancing antioxidant defenses, Centella Asiatica leaf may help protect kidney tissues from oxidative damage. Inflammation is another key factor in diabetic kidney injury. Increased levels of pro-inflammatory molecules, such as cytokines and chemokines, contribute to immune cell recruitment and amplification of inflammatory responses in the kidneys. Research has reported that Centella Asiatica leaf may suppress the production of these pro-inflammatory molecules in the kidneys of diabetic rats, indicating its potential as an anti-inflammatory agent[21]. By modulating the inflammatory response, Centella Asiatica leaf may help reduce kidney inflammation and subsequent tissue injury. Fibrosis, characterized by excessive accumulation of extracellular matrix components, is a hallmark of diabetic nephropathy. Centella Asiatica leaf has demonstrated the ability to inhibit the deposition of fibrotic markers, including collagen, in the kidneys of diabetic rats. By modulating extracellular matrix remodeling, Centella Asiatica leaf may help prevent the development of kidney fibrosis and maintain kidney structure and function. Furthermore, Centella Asiatica leaf has shown potential to preserve kidney function in diabetic rats. It has been found to reduce markers of kidney damage, such as blood urea nitrogen (BUN) and serum creatinine levels. These markers reflect kidney function impairment, and the observed decrease in response to Centella Asiatica leaf treatment indicates a protective effect on the kidneys. While the findings from this research are promising, it is important to note that this study was conducted using animal models. Translating these results to human applications requires further research and clinical trials. Additionally, individual variations, dosage, and treatment duration need to be considered. Therefore, consulting with healthcare professionals before considering the use of Centella

Asiatica leaf or other herbal treatments for diabetic kidney injury is crucial[22-24]. NGAL is a protein that serves as a biomarker for kidney injury and inflammation. Increased NGAL levels are often observed in diabetic nephropathy, indicating kidney damage. Research has explored the potential of Centella Asiatica leaf in modulating NGAL levels in the kidneys of diabetic rats. Studies conducted on rat models have shown that treatment with Centella Asiatica leaf extract can lead to a decrease in NGAL levels in the kidneys of diabetic rats. This suggests that Centella Asiatica leaf may have protective effects against kidney injury in diabetes.

The exact mechanism by which Centella Asiatica leaf affects NGAL levels is not fully understood. However, several explanations may be considered. Firstly, Centella Asiatica leaf has been shown to have antioxidant properties. Diabetes is associated with increased oxidative stress, which can cause kidney damage and albuminuria. By reducing oxidative stress, Centella Asiatica leaf may help protect the kidneys and prevent albumin leakage into the urine. Secondly, Centella Asiatica leaf has demonstrated anti-inflammatory effects in diabetic rat models. Inflammation plays a significant role in the development of diabetic nephropathy, and by suppressing the inflammatory response, Centella Asiatica leaf may help reduce NGAL levels. Inflammatory pathways can trigger the production and release of NGAL, and attenuation of inflammation by Centella Asiatica leaf may contribute to the observed decrease in NGAL levels. Additionally, Centella Asiatica leaf has shown potential to preserve kidney function in diabetic rats. As NGAL is closely related to kidney damage and dysfunction, the preservation of kidney function by Centella Asiatica leaf may indirectly lead to a decrease in NGAL levels[25,26]. Although the findings regarding the effects of Centella Asiatica leaf on NGAL levels in diabetic rat models are promising, it is important to note that further research is needed to fully understand the underlying mechanisms and to validate these findings in humans. Individual variations, dosage, and treatment duration should also be considered. Therefore, consulting with healthcare professionals is essential before considering the use of Centella Asiatica leaf or other herbal treatments to address NGAL levels in diabetic kidney injury. Albumin is a protein found in the blood and is commonly used as a marker to assess kidney function. In diabetic nephropathy, the kidneys become damaged, leading to increased albumin excretion in the urine, a condition known as albuminuria. Research has investigated the potential of Centella Asiatica in modulating albumin levels in the kidneys of diabetic rats. Studies conducted on rat models have shown that treatment with Centella Asiatica leaf extract can help reduce albuminuria in diabetic rats[27,28]. This indicates that Centella Asiatica leaf may have a protective effect on the kidneys and help maintain albumin levels. The exact mechanism by which Centella Asiatica leaf affects albumin levels is not fully understood. However, several explanations may be considered. Firstly, Centella Asiatica leaf has been shown to have antioxidant properties. Diabetes is associated with increased oxidative stress, which can cause kidney damage and albuminuria. By reducing oxidative stress, Centella Asiatica leaf may help protect the kidneys and prevent albumin leakage into the urine. Secondly, Centella Asiatica leaf has demonstrated anti-inflammatory effects in diabetic rat models. Inflammation plays a significant role in the development of diabetic nephropathy, and by suppressing the inflammatory response, Centella Asiatica leaf may help reduce albuminuria. Inflammatory pathways can lead to kidney damage and increased albumin excretion, and the anti-inflammatory effects of Centella Asiatica leaf may help mitigate these effects.

CONCLUSION

Based on the findings, it can be concluded that the ethanol extract of Centella asiatica (pegagan) leaves at a dose of 300 mg/kg body weight exhibited the most effective reduction in kidney injury markers, including KGD, KIM-1, NGAL, and albumin levels, compared to doses of 100 and 200 mg/kg body weight. These effects were also significantly different ($p<0.001$) compared to the group administered only nicotinamide and streptozotocin (STZ). Therefore, the 300 mg/kg body weight dose of pegagan leaf ethanol extract shows promising nephroprotective activity against kidney injury induced by nicotinamide and STZ.

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