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Reseacrh

Effect of Ethanolic Extract in *Moringa oleifera, Lam*. Leaf on Uric Acid Levels and Body Surface Area of Kidney Glomerulus in Wistar Rats (*Rattus novergicus*) Induced Metabolic Syndrome Model

Muhammad Dzaki Darmawan, Jarot Subandono, Novan Adi Setyawan, Dyah Ratna Budiani

Study Program of Medical Doctor Education, Faculty of Medicine, Universitas Sebelas Maret

ABSTRACT

Background: There has been an increasing prevalence of metabolic syndrome (MS) caused by life style such as sedentary behavior and western diet. Metabolic syndrome causes degeneration in ren's structure and processes the elimination of by product in metabolism, which is uric acid. *Moringa oleifera Lam*. leaves contain antioxidant that can repair damages caused by MS. Studies about improvement of ren's structure and uric acid level related to Moringa oleifera Lam. leaves' consumption has not been found yet. Therefore, this study was intended to examine the effects of ethanolic extract in *Moringa oleifera Lam*. leaves to uric acid and glomerular surface area in male wistar rat (*Rattus norvegicus*) with induced metabolic syndrome model.
Method: This study is an experimental laboratory study. The subjects of this study consisted of 30 rats which were divided into 5 groups with 6 in each group. K1 is control group, K2 is MS group, and K3, K4, and K5 are MS groups given variety of ethanolic extract doses. The induction of MS was done by giving high-fat diet in 28 days and injection of streptozotocin-nicotinamide (STZ-NA) in the 25th day. Rats in group K3, K4, and K5 were given doses of 150, 250, and 350 mg/kgBW in 28 days.
Results: The administration of high-fat diet for 28 days and injection of STZ-NA caused MS condition in rats. Repeated ANOVA and One-Way Anova test showed that the administration of ethanolic extract in Moringa oleifera Lam. leaves with doses of 150, 250, and 350 mg/kgBW in 28 days decreased uric acid significantly (p= 0.001; p=0.001; p= 0.001). Another result also found that ethanolic extract from *Moringa oleifera Lam*. leaves with doses of 250 and 350 mg/kgBW increased area of glomerular surface area in rats significantly.
Conclusion: The administration of ethanolic extract from *Moringa oleifera Lam*. leaves with doses of 150, 250, and 350 mg/kgBW for 28 days decreased uric acid level in rats. Ethanolic extract of *Moringa oleifera Lam*. leaves 250 and 350 mg/kgBw doses increase glomerular surface area.

Keywords: Moringa Oleifera, uric acid, glomerular cross-sectional area, metabolic syndrome, kidney

Correspondence:
Muhammad Dzaki Darmawan. Study Program of Medical Doctor Education, Faculty of Medicine, Universitas Sebelas Maret. Email: mdddzaki@student.uns.ac.id.

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BACKGROUND

Globalization and changing times have caused a shift in lifestyle and eating patterns that occur in society. This is known as sedentary behavior. People who consume traditional food are now accustomed to con-

suming instant and western food (Suhaema and Masthalina, 2015). Consumption of junk food, meat, fried food increases the incidence of metabolic syndrome (Suhaema and Masthalina, 2015; Czekajło et al., 2019). This condition occurs due to an increase in consumption of high calories but low in fiber, decreased physical activity, and the development of means of transportation (Saklaen, 2018).

Metabolic syndrome is an interconnected constellation of various physiological, biochemical, clinical, and metabolic factors that directly increase the risk of cardiovascular disease and type 2 diabetes mellitus (Kaur, 2014). Globally, the prevalence of metabolic syndrome is around 25% of the world's population (Saklaen, 2018). Meanwhile, the prevalence of metabolic syndrome in Indonesia is 21.66%, dominated by women and residents of urban areas (Herningtyas and Ng, 2019).

Diets high in carbohydrates and fats can induce metabolic syndrome, cardiovascular remodeling, hypertension, ventricular hypertrophy, conduction changes, endothelial dysfunction, degeneration of renal structures and an increase in the area of the islets of Langerhans (Panchal et al., 2011). Studies in wistar rats induced by a diet or high fat intake showed hypercholesterolemia which can reduce renal blood flow, glomerular filtration and ultrafiltration, and impair tubular excretion (Salim et al., 2018). Damage to the kidneys affects the process of eliminating the end product of metabolism in the form of uric acid (Sherwood, 2013).

Uric acid is the product of purine nucleotide degradation and has the ability to remove oxygen free radicals and protect erythrocyte membranes from lipid oxidation (Li, Hsieh and Chang, 2013). Metabolic syndrome is associated with an increased risk of hyperuricemia (Singh and Kari, 2013). Both of these, both the metabolic syndrome and hyperuricemia are closely related to hyperinsulinemia. Metabolic syndrome and hyperuricemia are associated with insulin resistance (Li et al., 2013). In a study with rats, it was found that reducing uric acid levels in obese rats could reduce insulin resistance (Baldwin et al., 2011). The imbalance of Reactive Oxygen Species (ROS) is referred to as oxidative stress which leads to many pathological conditions such as hypertension, ischemia, diabetes, obstructive pulmonary disease, and asthma (Birben et al., 2012).

There is an increase in the use of herbal remedies in the community which are considered non-toxic and have very few side effects (Gupta et al., 2012). Moringa plant is one of the plants used as herbal medicine. This plant is known to be rich in beneficial substances such as -carotene, protein, vitamin C, calcium, potassium, and acts as a natural source of antioxidants from ingredients such as ascorbic acid, flavonoids, phenolics, tannins, saponins and carotenoids (Toma and Deyno, 2014; Vergara-Jimenez et al., 2017). Substances that are nutritious for health are found in almost all components of the Moringa plant, including Moringa leaves.

Seeing the potential of this Moringa leaf, a study was carried out to determine the effect of the ethanolic extract of Moringa leaf (Moringa oleifera, Lam.) on uric acid levels and changes in the histopathological picture of the glomerular cross-sectional area of the kidney of Wistar rats (Rattus norvegicus) induced by STZ-NA and diet administration. high fat to achieve metabolic syndrome state.

SUBJECT AND METHOD

1. Study Design

This research was carried out in the form of an experimental laboratory study with a

pretest-posttest control group design and post-test only control group design because the blood uric acid levels were measured before and after being treated, while the measurement of the renal glomerular cross-sectional area was only carried out after the subject was given treatment. In this study, the induction of metabolic syndrome conditions and administration of Moringa leaf ethanolic extract was carried out at the Food and Nutrition Laboratory of the Center for Food and Nutrition Studies (PSPG) Gadjah Mada University Yogyakarta. Meanwhile, the painting and histopathological observations of kidney tissue were carried out at the Anatomical Pathology Laboratory, Faculty of Medicine, Sebelas Maret University, Surakarta.

2. Population and Sample

The research population was 30 Wistar rats (Rattus norvegicus) which were selected by purposive sampling. Inclusion criteria were male Wistar rats aged 2-3 months with a body weight of 150-200 grams.

3. Study Variables

The independent variable was the dose of the ethanolic extract of Moringa leaves (*Moringa oleifera, Lam.*). Dependent variable is uric acid level and renal glomerular cross-sectional area.

4. Variable Operational Definition

The independent variable was the dose of Moringa leaf ethanolic extract (Moringa oleifera, Lam.) using Moringa leaves obtained in dry conditions from Kalasan, Sleman, Yogyakarta. Simplicia making and extraction process were carried out at the Food and Nutrition Laboratory of PSPG UGM Yogyakarta. The ethanolic extract of Moringa leaves was extracted by maceration method using 70% ethanol solvent and then filtered into the filtrate. The extract was administered orally using a gastric probe at a dose of 150 mg/kgBW/day, 250 mg/kgBW/day, and 350mg/kgBW/day with CMC-Na solvent 2ml/200grBW from the 28th to the 56th day.

The dependent variable of uric acid level is blood uric acid level obtained through retroorbital vein puncture and then measured four times, namely on day 0 (after the adaptation process), day 25 (before the STZ-NA induction process), day 28 (after the STZ-NA induction process and high-fat diet), day 57 (before the termination process). The dependent variable of the renal glomerular cross-sectional area was the average glomerular cross-sectional area in the microscopic preparation of induced metabolic syndrome kidney tissue observed with an Olympus CX 22 light microscope. The preparations were stained with Hematoxylin-Eosin (H&E stain) and observed in nine fields of view with a magnification of 100x. and 400x in each kidney.

5. Data Analysis

Uric acid level data were tested using the Repeated ANOVA test with Bonferroni post-hoc and also One-way ANOVA with post-hoc Tukey HSD to see the difference in uric acid levels on day 0, day 25, day 28, and 57th day. Analysis of the glomerular cross-sectional area data was carried out using the Kruskal Wallis test with post-hoc Mann-Whitney to determine the effect of giving Moringa leaf ethanolic extract on the renal glomerular cross-sectional area.

6. Ethical Eligibility

This research has passed the ethical feasibility of the health research ethics commission of RSUD Dr. Moewardi Number: 1.039/-XI/HREC/2021 and Number: 10/I/-HREC/2021

RESULTS

1. Achievement of Metabolic Syndrome

Clinical parameters in this study showed an increase in body weight >8% from the initial condition, an increase in fasting blood sugar

(GDP) > 200mg/dL, an increase in blood sugar while (GDS) > 200 mg/dL, an increase in triglycerides > 150 mg/dL, low high-density lipoprotein (HDL) levels, and increased low-density lipoprotein (LDL) levels. Some of these parameters indicate the achievement of metabolic syndrome conditions.

2. Differences in Uric Acid Levels

Data on differences in uric acid levels from each group on day 28 (after high-fat diet and STZ-NA induction) and day 57 (after administration of Moringa leaf ethanolic extract) are shown in Table 1.

The Saphiro-Wilk normality test showed p>0.05 in all groups and the Repeated ANOVA test showed significant differences (p<0.005) in the treatment groups, namely groups K2, K3, K4, and K5. Post Hoc Bonferroni test results in table 2.

Table 1. Average Uric Acid Levels in Rats

Group	N	Day-28 (mg/dL)		Day-57 (mg/dL)	
		Mean	SD	Mean	SD
K1	6	1.80	0.10	1.84	0.08
K2	6	9.07	0.38	8.23	0.24
K3	6	8.97	0.49	5.29	0.35
K4	6	9.00	0.30	3.17	0.26
K5	6	8.94	0.19	2.06	0.08

Table 2. Bonferroni . Post Hoc Test Results

Group	p	Note
K1	<0.001	Significant
K2	<0.001	Significant
K3	<0.001	Significant
K4	<0.001	Significant
K5	<0.001	Significant

Table 3. Tukey HSD . Post Hoc Test Results

Group	p	Difference
K1 with K2	<0.001	Significant
K1 with K3	<0.001	Significant
K1 with K4	<0.001	Significant
K1 with K5	0.499	Non- Significant
K2 with K3	<0.001	Significant
K2 with K4	<0.001	Significant
K2 with K5	<0.001	Significant
K3 with K4	<0.001	Significant
K3 with K5	<0.001	Significant
K4 with K5	<0.001	Significant

To determine the difference in uric acid levels after administration of the ethanolic extract of Moringa leaves, a One-Way ANOVA test was carried out on the 57th day of uric acid levels in each group. The Saphiro-Wilk normality test showed p>0.05. There was a significant difference (p<0.05) between each group except for the K1 group and the K5 group. The results of the Post Hoc Tukey HSD test are in table 3.

3. Effect of Moringa Leaf Ethanolic Extract on Glomerulus Cross-sectional Area

An overview of the renal glomerular cross-sectional area is shown in table 4 and the average glomerular cross-sectional area in each group is shown in table 5.

Table 4. Overview of Glomerulus Cross-sectional Area with HE Painting at 100x and 400x . Magnifications

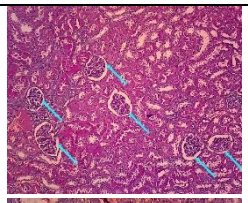
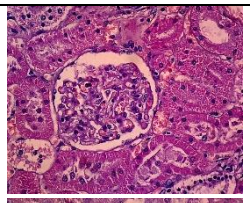
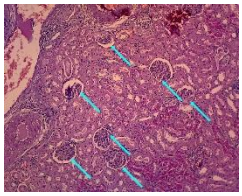
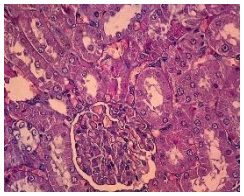
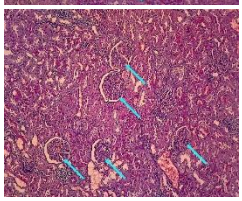
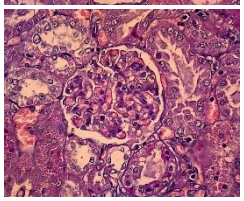
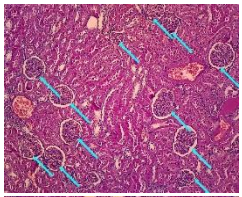
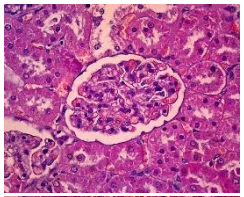
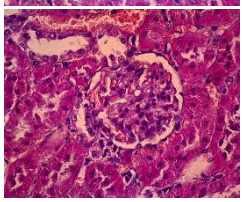
K	100x	400x
K1		
K2		
K3		
K4		
K5		

Table 5. Data on the Mean Cross-sectional Area of the Glomerulus of the Rat Kidney

Group	Cross-sectional Area of the Glomerulus of the Kidney (μm²)	
	Mean	SD
K1	3.88	0.87
K2	2.87	0.77
K3	3.60	1.00
K4	3.74	0.76
K5	3.74	0.76

The Kolmogorov Smirnov normality test showed $p<0.005$ in the K3 and K4 groups. Therefore, the Kruskal Wallis test was carried out to see the effect of the ethanolic extract of Moringa leaves on the cross-sectional area of the kidney glomerulus. The

p value <0.05 with a significance value of 0.029 means that there is a significant difference in each group. The results of the Mann-Whitney analysis test can be seen in table 6.

Table 6. Mann-Whitney Analysis Test Results

Group	p	Difference
K1 with K2	0.016	Significant
K1 with K3	0.337	Non- Significant
K1 with K4	0.630	Non- Significant
K1 with K5	0.631	Non- Significant
K2 with K3	0.055	Non- Significant
K2 with K4	0.004	Significant
K2 with K5	0.006	Significant
K3 with K4	0.936	Non- Significant
K3 with K5	0.873	Non- Significant
K4 with K5	1.000	Non- Significant

It was concluded that there was a decrease in the glomerular cross-sectional area on the administration of a high-fat diet and STZ-NA injection. This is evidenced by the significant difference between the K1 negative control group and the K2 group with metabolic syndrome.

There was an increase in the glomerular cross-sectional area when given the ethanolic extract of Moringa leaves at a dose of 150 mg/kgBW, but this increase was considered less significant when compared to the K2 metabolic syndrome group (p= 0.055). Meanwhile, in group K4 (administration of ethanolic extract dose of 250 mg/kgBW) and group K5 (administration of ethanolic extract dose of 350 mg/kgBW), there was a significant increase with p = 0.004 and p = 0.006 respectively.

4. Relationship of Glomerulus Cross-sectional Area with Uric Acid Level

To determine the relationship between glomerular cross-sectional area and uric acid levels, the Pearson correlation test was performed because both data on the mean glomerular cross-sectional area and uric acid levels on the 57th day were normally distributed on the Saphiro Wilk-test (p>0.05). The results of the Pearson correlation test can be seen in table 7.

Table 7. Pearson Correlation Test Results relationship between Glomerulus Cross-sectional Area and Uric Acid Levels on 57th Day Post Administration of Moringa Leaf Ethanolic Extract

Independent variable	r	p
Glomerulus cross-sectional area	-0.59	0.001

DISCUSSION

1. Achievement of Metabolic Syndrome

Achievement of metabolic syndrome conditions in accordance with the guidelines of the NCEP ATP-II (National Cholesterol Education Program-Third Adult Treatment Panel). Metabolic syndrome is defined when at least 3 of the 5 criteria are met, namely abdominal obesity, hyperglycemia, dyslipidemia, hypertension, and insulin resistance. It can be concluded that the K2, K3, K4, and K5 groups have reached a metabolic syndrome condition with hyperglycemia (GDP and GDS >200 mg/dL, dyslipidemia (triglycerides >150 mg/dL, elevated LDL, and HDL <35 mg/dL), as well as an increase in body weight >8% from its original condition.

2. Differences in Uric Acid Levels

After giving a high-fat diet and STZ-NA induction, there was a significant increase in uric acid levels in the K2-K5 treatment groups. This significant increase in uric acid levels proves that the administration of a high-fat diet and STZ-NA induction can cause a decrease in kidney function in the form of a decrease in the glomerular filtration rate (GFR) which leads to an increase in blood uric acid levels or hyperuricemia (Sah and Qing, 2015).

Measurement of uric acid levels on day 57 showed significant results in that the administration of Moringa leaf ethanolic extract could significantly reduce uric acid levels in experimental animals. In the K3 group, the average decrease in uric acid levels showed Mean= 5.29; SD= 0.35 ($p< 0.001$), the K4 group showed Mean= 3.17; SD= 0.26 ($p< 0.001$), and the K5 group showed Mean= 2.06; SD= 0.08 ($p<0.001$). The significance value of these three groups <0.05 indicates that there is a significant difference in uric acid levels before and after administration of Moringa leaf ethanolic extract.

From these results, it can be concluded that the ethanolic extract of Moringa leaves is able to significantly reduce uric acid levels. Giving Moringa leaf ethanolic extract at a dose of 150 mg/kgBW, 250 mg/kgBW, and 350 mg/kgBW can reduce uric acid levels.

Moringa leaf ethanolic extract can reduce uric acid levels through several mechanisms. The content of flavonoids in this case quercetin and kaempferol, alkaloids, tannins, and saponins can inhibit the synthesis of xanthine oxidase resulting in a decrease in uric acid levels (Pribadi and Widiartini, 2019). The most common mechanism of inhibition is through the n-hexane pathway. If this pathway is inhibited, then xanthine oxidase cannot convert hypoxanthine into uric acid so that uric acid levels decrease (Yumita et al., 2013).

In addition, flavonoids (quercetin and kaempferol) are nephroprotectors because of their ability to inhibit oxidative stress and inflammatory reactions in renal tubular cells. This protection from kidney function triggers the kidneys to excrete excess uric acid so that uric acid levels are in the normal range (Verzola et al., 2014). The content of vitamin C in Moringa leaves also increases the ability of kidney uric acid excretion (Anandagiri, Manuaba and Suastuti, 2014).

3. Effect of Moringa Leaf Ethanolic Extract on Glomerulus Cross-sectional Area

In the measurement of the glomerular cross-sectional area of experimental animals, the average result in group K1 was 3.88±0.87 m2, group K2 was 2.87±0.77 m2, group K3 was 3.60±1.00 m2, group K4 was 3.74±0.76 m2, and the K5 group was 3.71±0.85 m2. The cross-sectional area of the glomerulus in the K2 group decreased significantly when compared to the K1 group ($p= 0.016$).

Giving Moringa leaf ethanolic extract at a dose of 150 mg/kgBW (K3 group), 250 mg/kgBW (K4), and 350 mg/kgBW (K5) was able to increase the glomerular cross-sectional area when compared to the K2 group which was not given ethanolic leaf extract. moringa. In the K3 group with a dose of ethanolic extract of Moringa leaves at a dose of 150 mg/kgBW, there was an increase in glomerular area but not significantly. This is evidenced by the significance value of the K3 group when compared to the K2 group ($p = 0.055$). While in groups K4 and K5 given a dose of ethanolic extract of Moringa leaves at a dose of 250 mg/kgBW and 350 mg/kgBW, there was a significant increase with a significance value of $p= 0.004$ and $p=0.006$, respectively, when compared to the K2 group. The increase that occurred in the K3, K4, and K5 groups was

close to normal in the original condition in the negative control group (K1 group). This is evidenced by the absence of a significant difference with a significance value of p>0.05 in the K3 group (p= 0.337), the K4 group (p= 0.630), and the K5 group (p= 0.631) when compared to the negative control group (the negative control group). K1).

Dyslipidemia, insulin resistance, obesity and hypertension can increase the expression of adipositokines, angiotensin, and also pro-inflammatory cytokines that can cause kidney fibrosis (Singh and Kari, 2013). Obesity and metabolic syndrome will increase Angiotensin II which will activate NADPH oxidase (NOX) and increase ROS. These ROS will later cause damage to the endothelium (Rochlani et al., 2017). Insulin resistance can trigger pro-inflammatory cytokines in the kidney which results in mesangial expansion, basement membrane thickening, podocytopathy, and also loss of slit pore diaphragm integrity (Singh and Kari, 2013).

The state of the metabolic syndrome can also activate the renin-angiotensin-aldosterone system (RAAS) which can cause glomerular damage. There is an increase in glomerular pressure caused by an increase in renal arterial blood pressure. This results in an increase in glomerular hydrostatic pressure. To prevent excessive capillary dilation, the kidneys compensate by depositing the mesangial matrix, thickening the basement membrane, and causing renal fibrosis. These structural changes result in a decrease in the filtration area in the kidney (Hall et al., 2014).

The antioxidant content of Moringa leaves can eliminate free radicals by accepting or donating electrons so as to produce new molecules that are non-reactive and harmless so as to reduce damage to kidney cells. In addition, the flavonoid content in Moringa leaves can increase the speed of glomerular filtration. Increased glomerular filtration rate can cause the release of substances that have accumulated in the kidneys more quickly so that urinary activity increases and reduces the accumulation in the kidneys. The content of quercetin can also improve inflammation and fat in the kidneys of rats (Wicaksana, 2017).

The results of this study are different from similar studies conducted in 2019, giving Moringa root ethanolic extract at a dose of 150 mg/kgBW and 350 mg/kgBW decreased the cross-sectional area of the glomerulus when compared to mice that were not given Moringa root ethanolic extract. At a dose of 250 mg/kgBW there was a non-significant increase in glomerular area (Azzahra, 2019). Chronic kidney disease is characterized by the deposition of the pathological matrix in the interstitial spaces and in the walls of the glomerular capillaries. This is a process of fibrogenesis which is believed to be a wound healing process from tissue damage that does not improve. As chronic kidney disease progresses, the fibrotic matrix expands and the nephrons and their supporting capillaries are lost, resulting in reduced kidney volume and impaired perfusion (Duffield, 2014).

4. Relationship between Glomerulus Cross-sectional Area and Uric Acid Level

The results of this study indicate that an increase in glomerular area reduces uric acid levels. In the early phase after STZ-NA induction, there is glomerular hypertrophy, an increase in the glomerular filtration rate, an increase in intraglomerular pressure and microalbuminuria which can cause hyperfiltration in the glomerulus (Maric and Hall, 2011). Hyperfiltration conditions can affect uric acid levels. In the advanced phase, structural changes in the glomerulus such as expansion of the mesangial matrix, thick-

ening of the basement membrane, and renal fibrosis can reduce the area and also the glomerular filtration rate. This can lead to an increase in uric acid levels (Hall et al., 2014; Storhaug et al., 2015).

Giving Moringa leaf ethanolic extract was able to reduce uric acid levels and increase the glomerular cross-sectional area of the kidneys of Wistar rats model of induced metabolic syndrome. Moringa leaves have good potential as a nephro-protector agent, preventing hyperuricemia and preventing chronic kidney disease depending on the dose given.

AUTHORS CONTRIBUTION

Muhammad Dzaki Darmawan, Jarot Subandono, Novan Adi Setyawan, and Dyah Ratna Budiani collected and analyzed data and wrote manuscripts.

CONFLICT OF INTEREST

The author declares that this study was carried out without any commercial interest or funding.

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REFERENCE

Anandagiri DDAWM, Manuaba IBP, Suastuti NGAMDA. (2014) "Pemanfaatan Teh Kombucha Sebagai Obat Hiperurisemia Melalui Pengahmbatan Aktivitas Xantin Oksidase pada Rattus norvegicus (Utilization of Kombucha Tea as a Hyperuricemia Drug Through Inhibition of Xanthine Oxidase Activity in *Rattus norvegicus*). Jurnal Kimia. 5(2): 40–51. Tersedia pada: https://research.kombuchabrewers.org/wp-content/uploads/kkresearch-files/pemanfaatan-tehkombucha-sebagai-obat-hiperurisemia-melalui-penghambatan-aktifitas-xantinoksidase-p.pdf.

Azzahra KR. (2019) "Pengaruh Pemberian Ekstrak Etanolik Daun Kelor (Moringa oelifera, Lam.) terhadap Kadar Kreatinin dan Luas Penampang Glomerulus: Tikus Putih (Rattus norvegicus) Model Sindrom Metabolik dengan Induksi STZ-NA dan Diet Tinggi Lemak (Effect of Ethanolic Extract of Moringa Leaves (Moringa oelifera, Lam.) on Creatinine Levels and Glomerular Cross-sectional Area: White Rat (Rattus norvegicus) Metabolic Syndrome Model with STZ-NA Induction and High Fat Diet)," Skripsi.

Baldwin W, McRae S, Marek G, Wymer D, Pannu V, Baylis C, Johnson RJ, et al. (2011). Hyperuricemia as a mediator of the proinflammatory endocrine imbalance in the adipose tissue in a murine model of the metabolic syndrom. Diabetes, 60(4): 1258–1269. doi: 10.2337/db10-0916.

Birben E, Sahiner UM, Sacksesen C, Erzurum S, Kalayci O (2012). Oxidative stress and antioxidant defense. World Allergy Organ J. 5(1): 9–19. doi: 10.1097/WOX.0b013e3182439613.

Czekajło A, Różańska D, Zatońska K, Szuba A, Rugulska-Ilow B. (2019). Association between dietary patterns and metabolic syndrome in the selected population of Polish adults - Results of the PURE Poland Study. Eur J Public Health, 29(2): 335–340. doi: 10.1093/eurpub/cky207.

Duffield JS. (2014). Cellular and molecular mechanisms in kidney fibrosis. J Clin

Invest, 124(6): 2299. doi: 10.1172/-JCI72267.a.

Gupta R, Mathur M, Bajaj VK, Katariya P, Yadav S, Kamal R, Gupta RS (2012). Evaluation of antidiabetic and anti-oxidant activity of Moringa oleifera in experimental diabetes. J Diabetes, 4(2): 164–171. doi: 10.1111/j.1753-0407.2011.00173.x.

Hall ME, do Carmo JM, da Silva AA, Juncos LA, Wang Z, Hall JE (2014). Hypertension and chronic kidney disease. Int J Neprol Renovasc Dis. 7: 75-88. doi: 10.2147/IJNRD.S39739.

Herningtyas EH, Ng TS (2019). Prevalence and distribution of metabolic syndrome and its components among provinces and ethnic groups in Indonesia. BMC Public Health, 19(1): 1–12. doi: 10.1186/s12889-019-6711-7.

Kaur J (2014). A comprehensive review on metabolic syndrome. Cardiol Res Pract. doi: 10.1155/2014/943162.

Li C, Hsieh MC, Chang SJ. (2013). Metabolic syndrome, diabetes, and hyperuricemia. Curr Opin Rheumatol, 25(2): 210–216. doi: 10.1097/BOR.0b013e3-2835d951e.

Maric C, Hall JE. (2011). Obesity, Metabolic syndrome and diabetic nephropathy. Contrib Nephrol, 170: 28–35. doi: 10.1159/000324941.

Panchal SK, Poudyal H, Iyer A, Nazer R, Alam A, Diwan V, Kauter K, et al. (2011). High-carbohydrate high-fat diet-induced metabolic syndrome and cardiovascular remodeling in rats. J Cardiovasc Pharmacol, 57(1): 51–64. doi: 10.1097/FJC.0b013e3181feb90a.

Pribadi FW, Widiartini C (2019). The Effect of Kelor Leaves (*Moringa oleifera*) Ethanol Extract on Serum Uric Acid and Tumor Necrosis Factor-α of Hyperuricemic White Rats (*Rattus norvegicus*). IOP Conference Series: Earth and Environmental Science, 406(1). doi: 10.1088/1755-1315/40-6/1/012006.

Rochlani Y, Pothineni NV, Kovelamudi S, Mehta JL (2017). Metabolic syndrome: pathophysiology, management, and modulation by natural compounds. Ther Adv Cardiovasc Dis. 11(8): 215–225. doi: 10.1177/1753944717711379.

Sah OSP, Qing YX. (2015). Associations between hyperuricemia and chronic kidney disease: A review. Nephrourol Mon, 7(3). doi: 10.5812/numonthly.-(3)2015.27233.

Saklayen MG. (2018). The Global Epidemic of the Metabolic Syndrome. Curr Hypertens Rep. 20(2), pp. 12. doi: 10.1007/s11906-018-0812-z.

Salim HM, Kurnia LF, Bintarti TW, Handayani (2018). The Effects of High-fat Diet on Histological Changes of Kidneys in Rats. BHSJ, 1(2): 109. doi: 10.20473/bhsj.v1i2.9675.

Sherwood, L. (2013) Introduction to Human Physiology.

Singh AK, Kari JA (2013). Metabolic syndrome and chronic kidney disease. Curr Opin in Nephrol Hypertens, 22(2): 198–203. doi: 10.1097/MNH.-0b013e32835dda78.

Storhaug HM, Toft I, Norvik JV, Jenssen T, Eriksen BO, Melsom T, Løchen ML, et al. (2015). Uric acid is associated with microalbuminuria and decreased glomerular filtration rate in the general population during 7 and 13 years of follow-up: The Tromsø Study BMC Nephrol, 16(1): 1–10. doi: 10.1186/-s12882-015-0207-1.

Suhaema, Masthalina H (2015). Pola Konsumsi Dengan Terjadinya Sindrom Metabolik di Indonesia (Consumption Patterns with the Occurrence of Metabolic Syndrome in Indonesia). Public health, 9(4): 340–347.

Toma A, Deyno S. (2014). Phytochemistry and Pharmacological Activities of Moringa Oleifera. IJP. 1(4): 222–253. doi: 10.13040/IJPSR.0975-8232.1(4).-222-31.

Vergara-Jimenez M, Almatrafi MM, Fernandez ML (2017). Bioactive components in Moringa oleifera leaves protect against chronic disease. Antioxidants, 6(4): 1–13. doi: 10.3390/-antiox6040091.

Verzola D, Ratto E, Villaggio B, Parodi EL, Pontremoli R, Garibotto G, Viazzi F. (2014). Uric acid promotes apoptosis in human proximal tubule cells by oxidative stress and the activation of NADPH oxidase NOX 4. PLoS ONE, 9(12): 1–19. doi: 10.1371/journal.-pone.0115210.

Wicaksana R. (2017). Pengaruh Ekstrak Biji Kelor Terhadap Kadar Asam Urat dan Gambaran Histopatologi Ginjal Tikus Putih Sindrom Metabolik (Effect of Moringa Seed Extract on Uric Acid Levels and Kidney Histopathological Features of Metabolic Syndrome in White Rats).

Yumita A, Suganda AG, Sukandar EY (2013). Xanthine oxidase inhibitory activity of some Indonesian medicinal plants and active fraction of selected plants. International Journal of Pharmacy and Pharmaceutical Sciences, 5(2): 293–296.