Jurnal Riset Kesehatan

POTENTIAL OF JAMBLANG (Syzygium cumini L.) LEAF EXTRACT ON BODY WEIGHT OF WISTAR RATS METABOLIC SYNDROME MODEL

Ida Nurwati[a*] ; Risya Cilmiaty AR[b] ; Danus Hermawan[c] ; Betty Saptiwi[d] ; Dyah Ratna Budiani[e] ; Jarot Subandono[f] ; Martini[g] ; Muthmainah[h] ; Sarsono[i] ; Selfi Handayani[j]

[a,b,c,d,e,f,g,h,i,j] *Medical Faculty ; Universitas Sebelas Maret (UNS) ; Kolonel Sutarto ; Jebres ; Surakarta 57126 ; Indonesia*

Abstract

Jamblang (*Syzygium cumini L.*) leaves contain several phytochemical compounds. These phytochemicals are thought to have roles as antihyperglycemic, antihyperlipidemic, and antioxidant agents. This study aims to prove that there is an effect of giving ethanolic extract of jamblang leaves on body weight (BW) of metabolic syndrome (MS) Wistar rats induced by high-fat high-fructose diet (HFFD) and injection of Streptozotocin (STZ)-Nicotinamide (Na), to determine different doses effect on the weight of Wistar rats. Laboratory experimental research with pre-post test control group. Samples were 8 weeks male Wistar (*Rattus noverigicus*) weighing 150-200 grams chosen by purposive random sampling method. Thirty rats were divided into 5 groups, each consisting of 6 rats. Normal group, metabolic syndrome group, 3 treatment groups MS were given jamblang leaf extract 100 mg/KgBW, 150mg/KgBW, 200mg/KgBW for 28 days. Data were analyzed by one way ANOVA test and repeated ANOVA test. The study showed an ethanolic extract of Jamblang leaves can reduce weight loss in Wistar rats with a metabolic syndrome model, and that the best dose used in this experiment is 150 mg/kgBW per day in Wistar rats with a metabolic syndrome model.

Keywords: *Jamblang leaves; Weight; Metabolic syndrome; Rat*

1. Introduction

Metabolic syndrome is a serious problem in the health sector, and prevalence of metabolic syndrome globally and successively based on the diagnostic criteria of the National Cholesterol Education Program Expert Panel and Adult Treatment Panel III (NCEP-ATP III); World Health Organization (WHO); The International Diabetes Federation (IDF) was 43.83%; 63.58%; and 9.14%(Osei-yeboah et al., 2017). Meanwhile, in Indonesia itself 21.66% of the population suffers from metabolic syndrome (Herningtyas & Tian Sheng Ng, 2019). Metabolic syndrome is caused by a sedentary lifestyle which is an adaptation of a lifestyle with a western diet and lack of physical activity (Suhaema & Masthalina, 2015). The western diet has a composition that is too high in calories, low in fiber and high in fat,

especially saturated fatty acids and cholesterol, this diet causes an imbalance in nutritional intake and is a risk factor for the emergence of metabolic syndrome (Marianti, Utami, & Christijanti, 2013). Meanwhile, low physical activity can trigger ischemic heart disease and diabetes (Xiao, Dash, Morgantini, Hegele, & Lewis, 2016).

Excess body weight in metabolic syndrome conditions can trigger complications such as type 2 diabetes mellitus, stroke, and myocardial infarction(Syafitri, Arnelis, & Efrida, 2015). Body weight is one of the important parameters of the metabolic syndrome (Fan et al., 2019). Jamblang (*Syzigium cumini L.*) leaves are plants that contain active compounds of flavonoids, tannins, and polyphenols that have the potential as antioxidants (Marliani, Kusriani, & Sari, 2014). The content of flavonoids, triterpenoids and tannins in Jamblang leaves has an antihyperlipidemic effect (Singh, Singh, Sagar, & Das, 2018). The antioxidant and

*) Corresponding Author (Ida Nurwati)
E-mail: idanurwati@staff.uns.ac.id

antihyperlipidemic effects in Jamblang leaves have a function as anti-free radicals, inhibiting the process of oxidative stress, so as to improve blood lipid profiles through the mechanism of lipid peroxidation inhibition and suppression of Malondialdehyde (MDA) production, and ultimately can reduce excess body weight (obesity) (Marianti et al., 2013).

Jamblang leaves contain compounds that are considered to be used as candidates for adjuvant therapy for metabolic syndrome. Research on the effect of Jamblang leaf ethanol extract and the effect of different doses of the extract on body weight in metabolic syndrome has not been done much, for that researchers are interested in conducting research on the effect of Jamblang (*Syzygium cumini L.*) leaf ethanol extract on body weight of Wistar rats model MS.

2. Method

The research design is experimental with a pretest posttest with control group design. This study used Wistar rats (Rattus novergicus) from the Laboratory of the Center for Food and Nutrition Studies, Gadjah Mada University Yogyakarta (PSPG UGM) aged 8 weeks and weighing 150-200 grams. The number of rats used calculations from the Federer formula, which was 5 mice per group, but the researchers used 6 mice per group. Sampling was done by purposive random sampling, determining the rats per group by simple randomization. After adaptation rats were randomly divided into 5 groups. All groups were weighed (BW). Group I (control) was given standard BR-2 pellet feed (water, ash, protein, and crude fiber) ad libitum. Groups II, III, IV and V were made MS by being given standard feed of BR-2 pellets given ad libitum plus a high-fat high-fructose diet (HFFD) for 24 days and STZ-Na injection.

The composition of HFFD consists of 2 ml coconut oil mixed with 2% cholesterol and 1% cholic acid and fructose 0.36mg/200g BW. The HFFD diet was given orally as much as 1% of the rat's body weight using a gastric probe. Streptozotocin was injected intraperitoneally 45mg/kgBW single dose on day 22 and nicotinamide (Na) 110mg/kgBW single dose was given 15 minutes before STZ injection (Pari and Srinivasan, 2010). All groups were examined to determine the success of the Metabolic Syndrome Model consisting of BW, Blood glucose (BG), HDL, TG and LDL. Treatment groups (III, IV and V) after MS were given Jamblang leaf extract. The dose of Jamblang leaf extract used in this study is the same as the dose used in the research of Ningrum, Salim and Balqis (2017) is: 100 mg/kgBW/day, 150 mg/kgBW/day and 200 mg/kgBW/day for 28 days (Ningrum, Salim, & Balqis, 2017).

The extract given is made in the form of a suspension solution using a mixture of CMC -Na 0.5% and given orally 2 ml with a gastric probem (Stevani, 2016). Wistar rats' body weight was weighed once a week using a Mettler Toledo scale, ratio measurement scale, units of grams. The comparison of the weight of white rats between groups measured at one time was analyzed by the one way Anova test, while the comparison between the weight of white rats measured at one time with another time was analyzed by the repeated Anova test.

3. Result and Discussion

Supporting data for the metabolic syndrome model

The following is data from laboratory examination of blood and body weight of white rats after being induced by HFFD and STZ-NA.
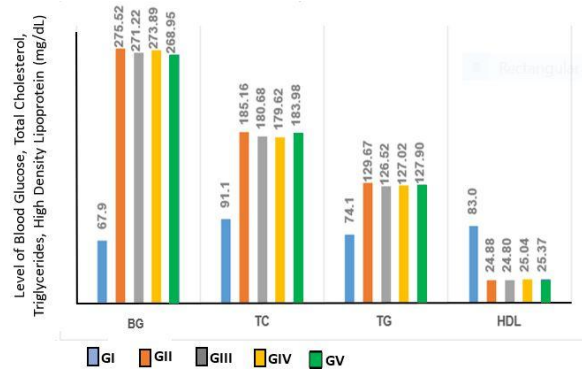
Figure 1. Comparison of Metabolic Syndrome Parameters Between Groups. Blood glucose: BG, TC: Kolesterol total, TG: Trigliserid

From the data table 1 show that white rats in groups G II, G III, G IV, and G V showed mean levels of Blood glucose >100 mg/dL, total cholesterol >110 mg/dL, and HDL <35 mg/dL. In addition, table 1 also shows that the weight gain of rats exceeds 8% of the initial weight. These data show that there are 4 criteria that have met the requirements as a determinant of the occurrence of metabolic syndrome based on Suman et al. (2015) and Tohman (2017). The data also means that induction with HFFD + STZ-Na in this study was successfully used to model the metabolic syndrome in white rats. White rats were weighed several times, namely: Before the metabolic syndrome model (H-) was made, after

the metabolic syndrome model was made but had not been treated with jamblang leaf extract (H0), and after the metabolic syndrome model was made and treated with jamblang leaf extract for 7 days, 14 days, 21 days, and 28 days, respectively (H 7, H 14, H 21, and H 28).

Table 1. Average weight before and after induction of HFFD + STZ-NA

Groups	Means of BW (gram) Before Induction of HFFD + STZ-NA	Means of BW (gram) After Induction	Addition of BW (%)
G I	168.67	197.67	17%
G II	170.83	210.17	23%
G III	172.50	211.33	22%
G IV	167.17	206.50	24%
G V	171.33	210.67	23%

From table 2 and figure 2 it can be seen that the rats in the G II group (which were modeled on the metabolic syndrome but did not receive the jamblang leaf extract) after H 0, their body weight decreased from time to time. Meanwhile, rats in groups G III, G IV, and G V (which were modeled on MS and treated with jamblang leaf extract), did not decrease in body weight but increased in line with alterations in body weight in the normal group (G I). These data indicate that jamblang leaf extract has an effect on inhibiting the occurrence of weight loss in metabolic syndrome rats. The effect is significant or not, it can be seen in the statistical test data.

Statistical analysis results

Table 2. Average Weight of White Rats Before and After being given Jambalang Leaf Extract

Groups	Means of BW (gram) ± SD					
	H-	H0	H7	H14	H21	H28
G I	168.6 ± 2.8	197.6 ± 2.1	204.1 ± 3.0	211.5 ± 2.4	218.6 ± 2.5	226.0 ± 2.6
G II	170.8 ± 4.9	210.1 ± 5.5	205.3 ± 5.9	200.1 ± 5.9	194.8 ± 4.9	188.8 ± 5.8
G III	172.5 ± 4.5	211.3 ± 4.6	214.5 ± 4.8	215.6 ± 8.3	219.6 ± 4.4	223.3 ± 5.0
G IV	167.17 ± 3.4	206.5 ± 2.7	209.3 ± 2.9	214.3 ± 3.5	219.5 ± 2.2	224.33 ± 3.6
G V	171.33 ± 3.9	210.6 ± 4.1	216.1 ± 4.9	220.8 ± 3.7	228.0 ± 4.2	234.6 ± 4.1

Homogenity tests showed that before induction of HFFD + STZ-Na p value = 0.701 and after induction of HFFD + STZ-Na p value = 0.107. The results of statistical analysis of the comparison of the weight of white rats between groups measured at one time were analyzed by the one way Anova test, all groups showed a significant difference (p = 0.001) while the comparison between the weight of white rats measured at one time and another time was analyzed by repeated tests. Anova. From the results of statistical tests concluded the following things:

a. One way Anova test followed by post hoc test showed that at H 14, H 21, and H 28, the body weight of the G II group rats was significantly lower than the G I group's body weight. The G II group is a group of rats modeled for the metabolic syndrome but not treated with jamblang leaf extract. The G I group was a group of normal mice. The results of these statistical tests showed that the model of the metabolic syndrome that was made, after lasting for at least 14 days could lead to significant weight loss. This result was also supported by the repeated Anova test which showed a significant weight loss over time (from H 0 to H 28) in G II group rats. Weight loss in group G II may be caused by a state of sustained/persistent hyperglycemia.

b. One way ANOVA test followed by post hoc test also showed that at H 14, H 21, and H 28, rats in group G III and G IV had significantly higher weight than group G II, and showed no significant difference compared to group G I. Meanwhile, the G V group rats showed a significantly higher body weight than the G II and G I groups. These results indicate that during H 14, H 21, and H 28 administration of jamblang leaf extract at a dose of 100

mg/kg BW in G III and a dose of 150 mg/kg BW in G IV could significantly inhibit the decrease (can increase) the weight of MS rats with results similar to the group of rats normal (G I). The administration of jamblang leaf extract at a dose of 200 mg/kg BW in G V can also significantly inhibit the decrease in the weight of MS rats, but the effect actually exceeds that of normal rats (G I). This may occur because the increase in the extract dose to 200 mg/kg BW actually exceeds the effective dose which can inhibit weight loss in MS rats, so that the increase in body weight that occurs exceeds normal conditions.

c. The repeated Anova test followed by a post hoc test in each group receiving jamblang leaf extract, namely G III, G IV, and G V almost all showed a significant increase in body weight over time (from H 0 to H 28). The picture of weight gain in the G III, G IV, and G V groups was in line with the increase in body weight that occurred in the G I group (normal rats). From the results of this statistical test, it can be concluded that jamblang leaf extract can inhibit the decrease (can increase) the body weight of metabolic syndrome rats from time to time.
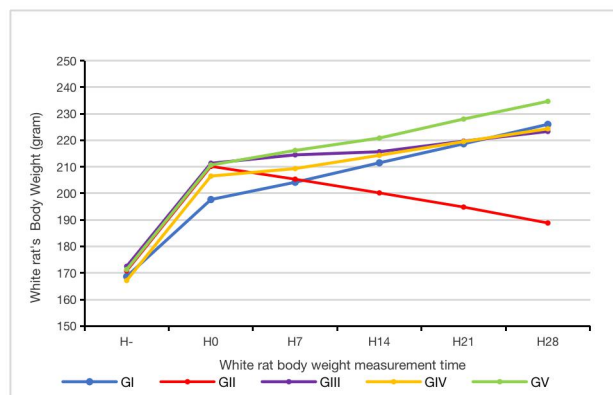
Figure 2. *Body weight alteration graph.*
H-: BW before the metabolic syndrome model was made. H0: BW when after making the BW model but has not received treatment with jamblang leaf extract. H7, H14, H21, H28: The weight of the white rats after the model was made and after administration of jamblang leaf extract for 7 days, 14 days, 21 days, and 28 days, respectively. GI: Normal control group, GII: Metabolic syndrome group without treatment with jamblang leaf extract, G III, G IV, and G V: The metabolic syndrome group, respectively, were given jamblang leaf extract at a dose of 100 mg/kg BW, 150 mg/kg BW, and 200 mg/kg BW.

Table 3. Describe Effects Size of Jamblang on body weights

Groups	H0	H28	Effects size (%)
GI	197.67	226.00	+12.54
GII	210.17	188.83	-11.30
GIII	211.33	223.33	+5.37
GIV	206.50	224.33	+7.95
GV	210.67	234.67	+10.23

Achievement of metabolic syndrome conditions in experimental animals

The research data in table 1 and the graph in figure 1 show that MS induction using HFFD feed and STZ-Na. injection in experimental animals proved successful in the G II, G III, G IV, G V groups compared to the normal control group (G I). This is indicated by the value of the 4 biochemical parameters determining MS which exceeds the normal limit. The normal range of MS-related biochemical profiles in male Wistar rats aged ±11 weeks were as follows; Blood Glucose (50-135 mg/dl), TC (86.19-129.52 mg/dl),

TG (47.57-108.11 mg/dl), HDL (35.00- 66.67 mg/dl)) (Ihedioha, Noel-Uneke, & Ihedioha, 2013).

Suman et al. (2015) argues that the results of experimental animal studies can be said to be positive for MS because they have fulfilled 4 of the 5 predetermined MS criteria, namely initial body weight, blood glucose levels reaching > 100 mg/dL, total cholesterol levels > 110 mg/dL, and HDL-C <35mg/dL (Suman, Mohanty, Borde, Maheshwari, & Deshmukh, 2016). This is also reinforced by Rohman's research (2017) where if 3 of the 5 criteria according to the NCEP-ATP III

diagnosis are met then it can be designated as MS, the criteria in question are obesity, hypertriglyceridemia and low HDL levels below normal values (Rohman, Lukitasari, Nugroho, & Widodo, 2017).

HFFD feeding according to the theory in experimental male Wistar rats can induce hyperglycemia, obesity, and dyslipidemia in a fairly short time span of 3-4 weeks (Wong, Chin, Suhaimi, Fairus, & Ima-Nirwana, 2016). Meanwhile, STZ-Na injection will strengthen the effect of HFFD in terms of maintaining insulin resistance through a cytotoxic mechanism against pancreatic beta cells which will trigger persistent hyperglycemic conditions, followed by heart and adipose tissue damage and increase the degree of oxidative stress, inflammation and endothelial dysfunction (Husna, Suyatna, Arozal, & Purwaningsih, 2019). The status of oxidative stress that continues to increase can cause adipose tissue dysregulation and is the beginning of the pathophysiology of MS, including hypertension and cardiovascular complications such as atherosclerosis (Fernández-Sánchez et al., 2011).

Similar studies also suggest that a high-fat diet causes insulin resistance in peripheral tissues due to lipotoxicity, whereas low-dose streptozotocin causes a mild defect in insulin secretion (Atanasovska et al., 2014). Rohman's research (2017) explains that the combination of low-dose STZ injection with high-fat and sucrose feeds can induce metabolic syndrome conditions in experimental animals similar to metabolic syndrome in humans with a duration of 8 weeks (Rohman et al., 2017). The combination of a high-fat and high-fructose diet has been shown to increase several parameters of MS in experimental animals three times higher than the control group, and two times higher than if only using a high-fructose diet (Gancheva, Zhelyazkova-Savova, Galunska, & Chervenkov, 2015).

Fructose is the main regulator of glucose absorption and glycogen synthesis in the liver (Wulansari & Wulandari, 2018). High amounts of fructose can enter the hepatic circulation as a lipogenic agent and cause insulin resistance and glucose tolerance (Hidayati et al., 2020). Excessive consumption of fructose results in an increase in the rate of glucose metabolism in the liver, followed by the accumulation of lipogenic TG and cholesterol that can trigger conditions such as glucose tolerance and insulin resistance (Wong et al., 2016). A high-fructose diet can trigger insulin resistance through a de novo lipogenesis process, the final product in the form of carbon from the fructolysis and glucolytic processes is broken down as a constituent of fat deposits in adipose tissue, then hydrolyzed as free fatty acids which can be the main precursor for the formation of excess triglycerides as a trigger condition. insulin resistance (Wulansari & Wulandari, 2018).

Body weight after 24 days of HFFD and STZ-Na induction

In this study, after the MS model was formed, over time, the hyperglycemia that occurred would cause oxidative stress, thereby exacerbating the pre-existing insulin resistance condition. Giacco and Brownlee (2010) explained that hyperglycemia can trigger the formation of excessive ROS, causing oxidative stress (Giacco & Brownlee, 2010). Oxidative stress is one of the factors that can cause insulin resistance (Shattat, 2014). In insulin resistance, insulin cannot work optimally in muscle, fat, and liver cells. In insulin resistance there is a disturbance in glucose uptake by cells, so glucose cannot enter the cells (Chhikara et al., 2018). Thus the cell cannot form energy from glucose. If the body does not get energy from glucose, then the body will process other substances such as fat and protein to produce energy. The fat and protein reshuffle can cause a decrease in body weight (Hsieh et al., 2016).

In Castro et al. (2015) also stated that insulin resistance can cause insulin action disorders in lipid metabolism in the form of increased lipolysis in adipocytes and disturbances in protein metabolism in the form of decreased protein synthesis in muscles (Castro et al., 2015). One way Anova test followed by post hoc test also showed that at H 14 , H 21, and H 28, the rats in the G III and G IV groups had significantly higher weight than the G II group, and showed a non-significant difference compared to the G I group. Meanwhile, the mice in the G V group showed a significantly higher body weight than the G II and G I groups. These results indicate that during H 14, H 21, and H 28 administration of jamblang leaf extract at a dose of 100 mg/kg BW in G III and a dose of 150 mg/kg BW in G IV could significantly inhibit the decrease in body weight of metabolic syndrome rats with results similar to normal rats (G I).

The administration of jamblang leaf extract at a dose of 200 mg/kg BW in G V also significantly inhibited the decrease in MS rats, but the effect actually exceeded the normal rat group (G I). This may be because the increase in the

extract dose to 200 mg/kg BW actually exceeds the effective dose which can inhibit weight loss in metabolic syndrome rats, so that the increase in body weight that occurs exceeds normal conditions.

Body weight is one of the determinants of metabolic syndrome in experimental animals. In the study, weight gain was found in all groups of experimental animals. Giving HFFD is thought to stimulate the hunger center in the body. Thus, the experimental animals that consume the HFFD will increase their appetite, especially if consumed for a relatively long time, this will trigger obesity. HFFD is a significant cause of overweight and obesity (Hidayati et al., 2020).

The content of HFFD given to experimental animals consisted of a mixture of 2 ml coconut oil mixed with 2% cholesterol, 1% cholic acid, and 0.36 g/200 g body weight fructose. The high-fat high-fructose diet (HFFD) was administered orally using a gastric probe with a composition of 1% of the total body weight of the rats. Then specifically on day 29, induction was combined with STZ-Na injection. The dose of Streptozotocin (STZ) was given as much as 45 mg/kgBW and Nicotinamide (Na) as much as 110 mg/kgBW.

Body weight after administration of jamblang leaf ethanolic extract

Alteration in body weight (BW) in group II after being induced by Na and STZ were caused by rats experiencing DM which is one of the signs of MS. This is because the rats suffer from diabetes mellitus due to STZ induction. Streptozotocin is a glucosamine-nitrosourea mixture. The chemical name of this compound is *2-deoxy-2-(3methyl-3-nitrosoureido-D-locopyranose* (C6H15N3O7). This compound can enter cells via glucose transporter (GLUT-2). Pancreatic cells have more GLUT- 2 more than other body cells so that STZ has selective toxicity to pancreatic cells (Driyah et al¸2019). DM mice (after MS) in this study also experienced weight loss. Alterations in body weight in DM patients were an early symptom of weight loss body because blood glucose cannot enter the cells so that it does not have fuel to produce energy and uses the patient's fat and muscle reserves so that the patient experiences weight loss. The weight loss is due to tissues experiencing insulin receptor resistance to break down fat to obtain alternative energy and Damage to organs such as the pancreas and kidneys results in weight loss (Ramic, Prasko, Mujanovic, & Gavran, 2016).

Jamblang leaf extract given to Groups III, IV, and V all experienced an increase in body weight.

The increase in body weight is caused by containing pharmacological effects to lower blood sugar levels and assist in the absorption of nutrients in the given diet so as to repair damaged organs in the body thereby increasing the weight of rats. Chhikara et al (2018) explained that Jamblang has the main bioactive components, namely myricetin, oxalic acid, gallic acid, citronellol, cyanidin diglucoside, hotrienol, phytosterols, flavonoids, carotenoids and polyphenols as micronutrients that can be useful for lowering blood glucose/hypoglycemic, anti-inflammatory, antianemic, antibacterial, antioxidant, antiallergic, hepatoprotective, hypolipidemic and antipyretic (Chhikara et al., 2018). The glycosides in jamun called Jamboline can lower blood glucose by inhibiting the metabolism of carbohydrates into glucose and increasing the production of beta cell insulin. The content of myricetin and its derivatives in jamblang leaves has been shown to enhance insulin signaling pathways in skeletal muscle and adipocytes and, to protect pancreatic cells from cytokine-induced cell death (Sari, 2017).

There was no significant difference in weight gain in this experiment, both in groups G III, G IV and G V when compared to G I (control) and there was a significant difference when compared to group II (MS). The highest dose in the metabolic syndrome model rats given in this experiment, which was 200 mg/kg/BW per day in the MS model rats, showed the highest weight gain (in the KP III group). The administration of Jamblang leaf ethanol extract can reduce blood glucose levels in white rats with the most effective dose for reducing blood glucose levels, namely a dose of 200 mg/kg BW with a result of 100.00 ± 8.34 mg/dL (Rahman, Oktomalioputri, & Irramah, 2020).

The increase in body weight in the experimental group after administration of the ethanol extract of Jamblang leaves was suspected because the ethanolic extract of Jamblang leaves contained glycosides, including diglycosides and tetraglycosides. Diglycosides and tetraglycosides are ghrelin receptor agonists (Hsieh et al., 2016). Ghrelin is the first neuroenteric peptide known to act as a peripheral hunger signaling molecule. Ghrelin increases GH secretion, food intake and weight gain when administered peripherally or centrally. Ghrelin produces a stronger feeding-stimulating effect than other origenic peptides except Neuropeptide Y (NPY) (Joshi, Paudel, & Upreti, 2019).

The results of this statistical test concluded that jamblang leaf extract could inhibit the

decrease (can increase) the body weight of metabolic syndrome rats over time. This can happen because jamblang leaf extract contains various compounds that can function as antioxidants, antidiabetics, and improve insulin resistance, namely as flavonoids, phenolic acids, triterpenoids, saponins, tannins and steroids. The conclusion of this study is that the extract of jamblang leaf through the content of various compounds that are antidiabetic can control the occurrence of hyperglycemia, through the content of compounds that act as antioxidants can reduce oxidative stress, and through compounds that can improve insulin resistance can increase glucose uptake into cells. With the increased uptake of glucose by cells, the formation of energy derived from glucose can be fulfilled so that there is no need to disassemble fat or protein as an energy-forming material. Thus weight loss can be inhibited. In this research, the weight should be calculated regularly, so that the weight changing can be monitored. The weakness in this research is there wasn't present metabolic syndrome parameters, and histopatological organ in the final research.

4. Conclusion and Suggestion

The conclusion of this study is that the ethanolic extract of Jamblang leaves can inhibit weight loss in Wistar rats with metabolic syndrome model and the optimal dose given in this experiment is 150 mg/kgBW per day in Wistar rats with metabolic syndrome model. In the future, it is necessary to carry out further research using more complete parameters, by examining the parameters of the metabolic syndrome and to test the toxicity of jamblang leaf extract.

5. Acknowledgments

6. References

Atanasovska, E., Tasic, V., Slaninka-Miceska, M., Alabakovska, S., Zafirov, D., Kostova, E., & Labacevski, N. (2014). Six week follow-up of metabolic effects induced by a high-fat diet and streptozotocin in a rodent model of type 2 diabetes mellitus. *Prilozi (Makedonska Akademija Na Naukite i Umetnostite. Oddelenie Za Medicinski Nauki)*, 35(1), 169–179.

Castro, A. V. B., Kolka, C. M., Kim, S. P., Bergman, R. N., Sinai, C., & Angeles, L. (2015). Obesity, Insulin Resistance and Comorbidities – Mechanisms of Association. *Arquivos Brasileiros de Endocrinologia e Metabologia*, 58(6), 600–609.

Chhikara, N., Kaur, R., Jaglan, S., Sharma, P., Gat, Y., & Panghal, A. (2018). Bioactive compounds and pharmacological and food applications of: Syzygium cumini-a review. *Food and Function*, 9(12), 6096 – 6115. https://doi.org/10.1039/c8fo00654g

Fan, J., Liu, Y., Yin, S., Chen, N., Bai, X., Ke, Q., & Xia, M. (2019). Small dense LDL cholesterol is associated with metabolic syndrome traits independently of obesity and inflammation. *Nutrition and Metabolism*, 16(1), 1 – 9. https://doi.org/10.1186/s12986-019-0334-y

Fernández-Sánchez, A., Madrigal-Santillán, E., Bautista, M., Esquivel-Soto, J., Morales-González, Á., Esquivel-Chirino, C., & Morales-González, J. A. (2011). Inflammation, oxidative stress, and obesity. *International Journal of Molecular Sciences*, 12(5), 3117 – 3132. https://doi.org/10.3390/ijms12053117

Gancheva, S., Zhelyazkova-Savova, M., Galunska, B., & Chervenkov, T. (2015). Experimental models of metabolic syndrome in rats. *Scripta Scientifica Medica*, 47(2), 14. https://doi.org/10.14748/ssm.v47i2.1145

Giacco, F., & Brownlee, M. (2010). Oxidative Stress and Diabetic Complications. *Circulation Research*, 107(9), 1058 – 1070. https://doi.org/10.1161/CIRCRESAHA.110.223545.Oxidative

Herningtyas, E. H., & Tian Sheng Ng. (2019). Prevalence and Distribution of Metabolic Syndrome and Its Components Among Provinces and Ethnic Groups in Indonesia. *BMC Public Health*, 19(377), 1–12.

Hidayati, L., Dwi, A., Widodo, W., Hidayat, B., Program, I. S., Java, E., & Airlangga, U. (2020). Animal Models with Metabolic Syndrome Markers Induced by High Fat Diet and Fructose. *Medical Laboratory Technology Journal*, 6(1), 13 – 20. https://doi.org/10.31964/mltj.v1i1.266

Hsieh, S., Chung, T., Li, Y., Lo, Y., Lin, N., Kuo, P., & Tzen, J. T. C. (2016). Ginkgoghrelins, unique acylated fl avonoid diglycosides in Folium Ginkgo, stimulate growth hormone secretion via activation of the ghrelin receptor. *Journal of Ethnopharmacology*, 193,

237 – 247. https://doi.org/10.1016/j.jep.2016.08.015

Husna, F., Suyatna, F. D., Arozal, W., & Purwaningsih, E. H. (2019). Model Hewan Coba pada Penelitian Diabetes. *Pharmaceutical Sciences and Research*, 6(3), 131–141. https://doi.org/10.7454/psr.v6i3.4531

Ihedioha, J. I., Noel-Uneke, O. A., & Ihedioha, T. E. (2013). Reference values for the serum lipid profile of albino rats (Rattus norvegicus) of varied ages and sexes. *Comparative Clinical Pathology*, 22(1), 93–99. https://doi.org/10.1007/s00580-011-1372-7

Joshi, M., Paudel, M., & Upreti, S. (2019). Therapeutic influence of Jamun (Syzygium cumini): A review. *Journal of Pharmacognosy and Phytochemistry*, 8(3), 1056–1059.

Marianti, A., Utami, N. R., & Christijanti, W. (2013). Aktivitas Antioksidan Madu Floral terhadap Profil Lipid Darah Tikus Putih Hiperlipidemik. *Jurnal Sains Dan Teknologi*, 11(1), 1–8.

Marliani, L., Kusriani, H., & Sari, I. (2014). Aktivitas Antioksidan Daun dan Buah Jamblang (Syzigium Cumini L.) Skeel. *Sains, Teknologi Dan Kesehatan*, 4(1), 201–206.

Ningrum, L. P., Salim, N., & Balqis, U. (2017). Pengaruh Ekstrak Daun Jamblang (Syzygium cumini L) Terhadap Histopatologi Hepar Tikus Putih (rattus norvegicus) Diabetes Melitus. *Jurnal Ilmiah Mahasiswa Veteriner*, 1(4), 695–701.

Osei-yeboah, J., Owiredu, W. K. B. A., Norgbe, G. K., Lokpo, S. Y., Gyamfi, J., Allotey, E. A., & Attah, F. A. (2017). The Prevalence of Metabolic Syndrome and Its Components among People with Type 2 Diabetes in the Ho Municipality , Ghana : A Cross-Sectional Study. *International Journal of Chronic Diseases*, 2017, 1–8.

Rahman, F., Oktomalioputri, B., & Irramah, M. (2020). Pengaruh Pemberian Ekstrak Daun Duwet (Syzygium cumini) Terhadap Gambaran Histologi Ginjal Tikus (Rattus novergicus) yang Diintoksikasi dengan Timbal Asetat. *Jurnal Kesehatan Andalas*, 9(1), 171–177.

Ramic, E., Prasko, S., Mujanovic, O. B., & Gavran, L. (2016). Metabolic Syndrome-Theory and Practice. *Mater Sociomed*, 28(1), 71–73. https://doi.org/10.5455/msm.2016.28.71-73

Rohman, M. S., Lukitasari, M., Nugroho, D. A., & Widodo, N. (2017). Development of an Experimental Model of Metabolic Syndrome in Sprague Dawley Rat. *Research Journal Of Life Science*, 04(01), 76–86.

Sari, A. N. (2017). Potensi Antioksidan Alami Pada Ekstrak Daun Jamblang (Syzigium cumini (L.) Skeels). *Eksakta*, 18(2), 107–112.

Shattat, G. F. (2014). A Review Article on Hyperlipidemia : Types , Treatments and New Drug Targets. *Biomedical & Pharmacology Journal*, 7(2), 399–409.

Singh, S., Singh, L., Sagar, B. P. ., & Das, M. (2018). Evaluation of Antihyperlipidemic Activity of Ethanolic Extract of Syzygium cumini in Triton X-100 Induced Hyperlipidemic Rats. *International Journal of Pharmacy & Pharmaceutical Research*, 12(3), 40–54.

Stevani, H. (2016). *Modul Bahan Ajar Cetak Farmasi-Praktikum Farmakologi* (1st ed.). Jakarta: Pusat Pendidikan Sumber Daya Manusia Kesehatan.

Suhaema, & Masthalina, H. (2015). Pola Konsumsi Dengan Terjadinya Sindrom Metabolik di Indonesia. *Jurnal Kesehatan Masyarakat Nasional*, 9(4), 340–347.

Suman, R. K., Mohanty, I. R., Borde, M. K., Maheshwari, U., & Deshmukh, Y. A. (2016). Development of an Experimental Model of Diabetes Co-Existing with Metabolic Syndrome in Rats. *Advances in Pharmacological Science*, 1–11. https://doi.org/10.1155/2016/9463476

Syafitri, V., Arnelis, A., & Efrida, E. (2015). Gambaran Profil Lipid Pasien Perlemakan Hati Non-Alkoholik. *Jurnal Kesehatan Andalas*, 4(1), 274–278. https://doi.org/10.25077/jka.v4i1.234

Wong, S. K., Chin, K. Y., Suhaimi, F. H., Fairus, A., & Ima-Nirwana, S. (2016). Animal models of metabolic syndrome: a review. *Nutrition and Metabolism*, 13(1), 1–12. https://doi.org/10.1186/s12986-016-0123-9

Wulansari, D. D., & Wulandari, D. D. (2018). Pengembangan Model Hewan Coba Tikus Diabetes Mellitus Tipe 2 dengan Induksi Diet Tinggi Fruktosa Intragastrik. *Media Pharmaceutica Indonesiana*, 2(1), 41–47.

Xiao, C., Dash, S., Morgantini, C., Hegele, R. A., & Lewis, G. F. (2016). Pharmacological targeting of the atherogenic dyslipidemia complex: The next frontier in CVD prevention beyond lowering LDL cholesterol. *Diabetes*, 65(7), 1767–1778. https://doi.org/10.2337/db16-0046