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Antidiabetic Activity of Ethanol-Water Fraction of Longjack Root (*Eurycoma longifolia* Jack.) in Streptozotocin-Nicotinamide Induced Rats

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Abstract: This study aims to determine the decrease in glucose levels, MDA levels, and histopathological appearance of the pancreatic organs of Wistar white rats after administration of the ethanol-water fraction of longjack root. This study used a completely randomized design with four treatment groups and six replications. The treatment consisted of normal control, negative control (Na-CMC 0.5% 5 ml/200 g body weight), positive control (glibenclamide 0.09 mg/200 g body weight), and treatment of the ethanol-water fraction of longjack root with a dose of 500 mg/kg body weight. The results showed that the ethanol-water fraction of longjack root at a dose of 500 mg/kg body weight had antidiabetic activity comparable to that of glibenclamide at a dose of 0.09/200 g body weight, namely blood glucose levels and MDA levels in white rats of 123.55 mg/dl and 2.83 nmol/ml. The results of histopathological analysis of the pancreas of white rats showed that administration of the ethanol-water fraction of longjack root could repair damage to the islets of Langerhans due to the administration of streptozotocin-nicotinamide.

Keywords: Longjack root; Blood glucose level; Diabetes mellitus; MDA levels; Pancreatic histopathology

Introduction

Diabetes mellitus is a metabolic disease characterized by high glucose levels in the blood or hyperglycemia (Liem et al., 2015). Hyperglycemia can trigger the formation of free radicals through glucose autooxidation, the formation of Advanced Glycation End-products (AGEs), and the increase in the activity of polyol pathways. That causes damage to the cell membrane system and cell death in body tissues. (Lofty et al., 2017; Prakosa et al., 2017; Suastuti et al., 2015).

Diabetes mellitus is known as the silent killer disease; this is because this disease can attack body organs. In addition, sufferers are also often unaware of the early symptoms of this disease (Hazni et al., 2021) Diabetes mellitus has become a global health problem, and its prevalence tends to increase rapidly (Rantung et al., 2015). Based on data from the International Diabetes Federation in 2021, the number of people with diabetes mellitus worldwide is 537 million adults (aged 20-79 years). It is expected to increase to 643 million people in 2030 and 783 million people in 2045 (IDF, 2021).

People with diabetes need a large amount of antioxidant intake. (Dompeipen et al., 2015). It is because the administration of antioxidants to people with diabetes mellitus is an effort to inhibit the production of intracellular free radicals or increase the ability of defense enzymes against free radicals to prevent the emergence of oxidative stress and vascular complications (Prawitasari, 2019). Diabetes mellitus treatment strategies at this time use various ways, one of which is the use of hepatoprotective drugs (Jurnalis et al., 2014). Hepatoprotectors are chemical compounds that protect and repair liver tissue damaged due to the influence of toxin compounds (Wiendarlina et al., 2018). Hepatoprotectors are often used as a deterrent to liver

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damage with their mechanism as antioxidants (Panjaitan et al., 2013).

In the world of ethnobotany, 800 types of medicinal plants can be used in the treatment of diabetes mellitus, one of the plants is longjack (Eurycoma longifolia Jack.) (Verma et al., 2018). Longjack has the shape of a shrub or tree, can reach 10 meters in height, has an odd-pinnate compound leaf type, and the stem has a yellow color with a hard bark texture and a bitter taste. Longjack is one of the endemic plants from West Borneo, which is classified into the Simaroubaceae family, which has high economic value and many benefits in the field of medicine for human health (Hidayati et al., 2021).

All parts of longjack can be used as a fever medicine, gingivitis, worm medicine, and tonic after childbirth (Khajinou & Jiraungkoorskul, 2016; Mohamed et al., 2015). The part of longjack that is often used is the root. It is because the root of longjack is rich in active components such as quassinoids consisting of eurycomanol, eurycomalactone, and eurycomanone, which have mechanisms as antioxidants (Mohamed et al., 2015). Some studies have reported that longjack has antidiabetic activity. The administration of ethanol extract of longjack leaves at a dose of 176.4 mg/200g body weight can reduce blood glucose and MDA levels of white mice Wistar strains induced by streptozotocin-nicotinamide (Panjaitan & Astuti, 2021). In addition, administering methanol extract of longjack root at doses of 210 mg/kg body weight and 420 mg/kg body weight can reduce blood glucose levels in mice induced with glucose (Fransisca et al., 2018). Additionally, the administration of methanol-water fraction of longjack root at a dose of 500 mg/kg body weight is also reported to have a hepatoprotective activity that has a mechanism as an antioxidant (Panjaitan et al., 2013). Therefore, this study was conducted using different preparations to determine the antidiabetic activity of the ethanol-water fraction of longjack root which was characterized by decreased blood sugar, MDA, and structural improvements. of the pancreas organ in white Wistar rats induced with streptozotocin-nicotinamide.

Method

Experimental Animals

The use of test animals in this study was carried out under standard guidelines approved by the Health Research Ethics Committee of the Faculty of Health Sciences, Respati University Yogyakarta, Indonesia (No: 192.3/FIKES/PL/VIII/2021). The experimental animals used in this study were 24 Wistar strain male white rats (Rattus norvegicus), aged 2-3 months, with a body weight of 150-200 gs. The acclimatization process of the test animals was carried out for seven days at the Food and Nutrition Study Laboratory of Gadjah Mada University Yogyakarta, Indonesia. Each rat is placed in 1 cage equipped with a food and drink holder.

Extraction and Partition

Longjack root samples for this study were obtained from a typical West Borneo medicine and spice shop (Telok Belangak). A total of 5 kg of longjack root samples were cleaned, cut, dried, and powdered into a size of 40 mesh macerated with 96% ethanol at room temperature for 3x24 hours. Furthermore, the macerated filtrate is concentrated using a vacuum rotavapor. After that, the ethanol extract of the longjack root is partitioned and stratified with chloroform and ethyl acetate so that the ethanol-water fraction of the longjack root is obtained.

Measurement of Blood Glucose Levels

This study used a complete randomized design consisting of four treatments and six repetitions. The first treatment is normal control (N) which is not given treatment. The second treatment was a negative control (K-) given a 0.5% Na-CMC treatment (Sigma-Aldrich, sodium carboxymethyl cellulose, Missouri, USA) at a dose of 5 ml / 200 g body weight. The third treatment was a positive control (K+) given the glibenclamide (PT. Indofarma, glibenclamide, Bekasi, Indonesia) at a dose of 0.09 mg / 200g body weight. The fourth treatment was the ethanol-water fraction treatment of longjack root at a dose of 500 mg/kg body weight (P1).

On the first day, blood glucose levels were measured in all experimental animals. The blood draw is taken through the sinus orbitalis and then measured with a spectrophotometer. Before measuring blood glucose levels, experimental animals were fed for 10-12 hours and still given a drink. Furthermore, the experimental animals in treatment second, third, and fourth groups were induced streptozotocin-nicotinamide. The dose of streptozotocin used was 45 mg/kg body weight (Cayman Chemical, Streptozotocin, Ann Arbor, MI, USA). In comparison, the dose of nicotinamide used was 110 mg/kg body weight (Sigma-Aldrich, Nicotinamide, Missouri, USA) (Gashemi et al., 2014).

On the first, second, and third days, the experimental animals were not treated but fed and drank ad libitum. On the fourth day, the second blood glucose level was measured. Experimental animals were declared affected by diabetes when the blood glucose levels were 200 mg/dl. (Gashemi et al., 2014). The ethanol-water fraction of longjack root was administered to the experimental animals from the fourth day until the 17th day.

Measurement of MDA Levels

On the 18th day, all experimental animals were satisfied to eat for 10-12 hours while still being given a

drink. Then blood was taken through the sinus orbitalis and centrifuged until serum was obtained. Furthermore, serum measurements of MDA levels using the thiobarbituric acid (TBA) method.

Manufacture of Pancreatic Histopathological Preparation

Animals are dislocated cervically, then dissected and taken into pancreatic organs. Next, samples of pancreatic organs are washed with physiological NaCl solution and then fixed with a 10% formalin buffer. Furthermore, the pancreas organs will be carried out to make preserved preparations through the process of dehydration, purification, infiltration, planting in paraffin media, brushing, staining with hematoxylin-eosin dyes, and mounting.

Statistical Analysis

Analysis of blood glucose levels and MDA levels was carried out using one-way ANOVA with a normality test and data homogeneity test. If the data obtained are normally distributed and homogeneous, then proceed with the Tukey test. If the data obtained are not homogeneous, then the ANOVA cannot be continued so the Kruskal-Wallis test is carried out. Furthermore, to see the treatment group that there are real differences, it is continued with the Mann-Whitney test. Data on the histopathological picture of the pancreas were analyzed descriptively.

Result and Discussion

Result

Blood Glucose Levels

The results of blood glucose measurement showed that on day 0 all treatment groups had normal blood glucose levels, on day 4 an increase in blood glucose levels in the treatment of 0.5% Na-CMC, glibenclamide, and the ethanol-water fraction of longjack root, on day 18 showed a decrease in blood glucose in the treatment of the ethanol-water fraction of longjack root which was not statistically significantly different from the treatment of glibenclamide (P>0.05) whereas in the administration of 0.5% Na-CMC did not show a decrease in blood glucose. The results of measuring blood sugar levels in white rats can be seen in Table 1.

Table 1. The measurement results of blood glucose levels

Trial Group	Blood Glucose Levels (mg/dl)		
	Day 0	Day 4	Day 18
Normal Control	71.02^{a} ± 1.17	71.96^{a} ± 1.05	73.49a ± 0.86
Na-CMC 0,5% 5 ml/200 g BW	71.97^{a} ± 1.73	282.06^{b} ± 2.12	283.45c ± 2.08
Glibenclamide 0.09 mg/200 g BW	69.57^{a} ± 1.83	281.36^{b} ± 2.56	124.26b ± 1.69
Longjack root ethanol-water fraction 500 mg/kg BW	70.20^{a} ± 2.48	279.87^{b} ± 3.30	123.55b ± 3.58

Note: Data were presented as the mean ± standard deviation. Columns given the same letter are not significantly different (p>0.05).

MDA Levels

The results of the measurement of MDA levels showed that the MDA levels in the treatment group receiving 0.5% Na-CMC were higher than those receiving glibenclamide, while in the treatment group receiving the ethanol fraction- long root water, decreased MDA levels which were not statistically significantly different from glibenclamide treatment (P>0.05). The results of MDA levels in white rats on day 18 can be seen in Table 2.

Table 2. The measurement results of MDA levels

Trial Group	MDA Levels (nmol/ml)
Normal Control	1.71^{a} ± 0.18
Na-CMC 0,5% 5 ml/200 g BW	9.66^{c} ± 0.19
Glibenclamide 0.09 mg/200 g BW	3.02^{b} ± 0.28
Longjack root ethanol-water fraction 500 mg/kg BW	2.83^{b} ± 0.14

Note: Data were presented as the mean ± standard deviation. Columns given the same letter are not significantly different (p>0.05).

Histopathological Overview of White Rat Pancreatic Organs

The results of histopathological analysis of pancreatic organs in white rats showed that in the normal control treatment, normal islands of Langerhans structure were observed, characterized by β-pancreatic cells with good-looking round nuclei, and no cell degeneration and necrosis were observed. found, in treatment with Na-CMC 0.5% showed damage to the structure of islets of Langerhans which was characterized by degeneration and necrosis, there was discoloration of intercellular boundaries, cytoplasmic vacuolation, and β cells -pancreatic cells were found with enlarged nuclei and visible nucleoli, in glibenclamide treatment there was an improvement in the structure of the islets of Langerhans characterized by the monomorphic form of pancreatic β-cells, few degenerated cells were found with fading intercellular boundaries, as well as β- pancreatic cells with enlarged nuclei and visible nucleoli, in the treatment of an ethanol-water fraction of longjack root at a dose of 500 mg/kg BW showed an improvement in the structure of islets of Langerhans which was characterized by the

monomorphic form of pancreatic β-cells with round nuclei, found few cells with enlarged nuclei with visible nucleoli, and no necrotic cells. The results of the histopathological picture of the pancreas of white mice can be seen in Figure 1.

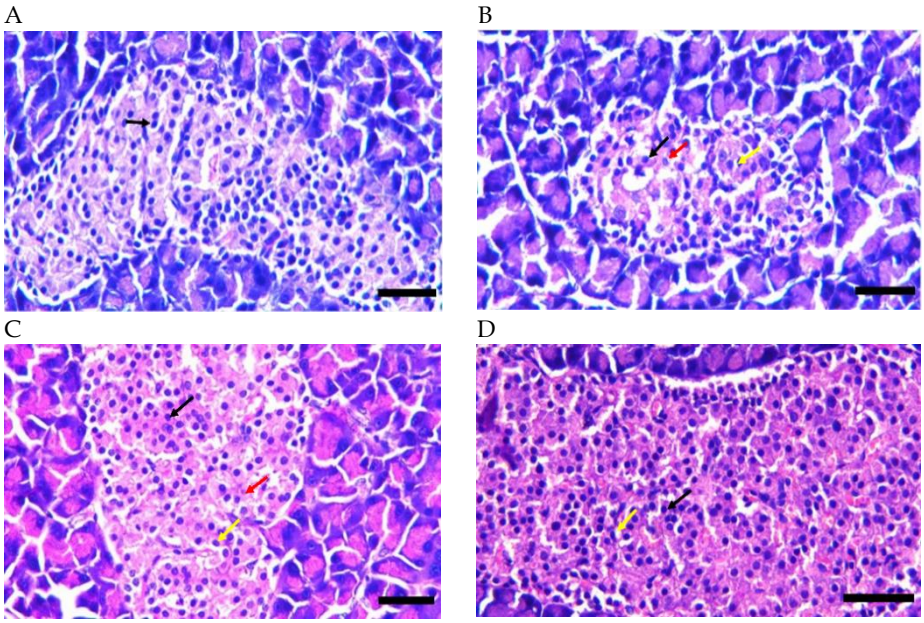

Figure 1. Histopathological overview of the pancreas organs (400X), (A) normal control; (B) negative control; (C) positive control; (D) The administrasion of ethanol-water fraction of longjack root (→) normal beta cells, (→) degenerated beta cells, and (→) necrotic beta cells.

Discussion

Diabetes mellitus is one of the metabolic diseases characterized by hyperglycemia. Hyperglycemia is a condition in which blood glucose levels in the blood plasma exceed normal limits. Therefore hyperglycemia is a basis for establishing the diagnosis of diabetes mellitus. (Fatimah, 2015; Putri et al., 2017). Hyperglycemia in diabetes can increase the production of free radicals in cells. It is caused by the autooxidation process, which triggers the formation of free radicals with the secretion of ROS (Reactive Oxygen Species), which damages cell membranes by converting the lipid structure of cell membranes into lipid peroxides. (Prakosa et al., 2017; Arief & Widodo, 2018).

Free radical countermeasures can use antioxidants. Antioxidant activity can capture free radicals that cause damage to pancreatic beta cells so that the remaining beta cells can function. Antioxidants are thought to protect normal pancreatic beta cells so that they can allow cell regeneration through mitosis or the formation of Langerhans islets through proliferation and endocrine differentiation. (Suryani et al., 2014). The regeneration of pancreatic beta cells can increase the secretion of the hormone insulin in the body, which can bring blood glucose into the cells, which can lower blood sugar (Khairan et al., 2018).

Based on the results of measuring blood glucose levels shown in Table 1, on day 0, normal rats' average blood glucose level ranged from 69.57 – 71.97 mg/dl. According to a previous study, normal rat blood glucose levels ranged from 50 – 135 mg/dl (Puspitasari & Syauqy, 2015). These groups showed that all animal models did not have diabetes without STZ- NA induction (Panjaitan & Astuti, 2021). On the fourth day, a second blood glucose level measurement was taken to determine the increase in blood glucose levels after being induced with STZ-NA with a dose of STZ 45 mg/kg berat badan and a dose of NA 110 mg/kg berat badan. Based on the results of these measurements, it is known that the average blood glucose level of rats in the Na-CMC 0.5%, glibenclamide, and the ethanol-water fraction of longjack root ranged from 279.86 – 282.06 mg / dL, this shows that all experimental animals had type 2 diabetes mellitus. According to the previous study, it was stated that if blood glucose levels in rats >250 mg/dl after STZ-NA injection, it was shown that all rats had type 2 diabetes mellitus (Ghasemi et al., 2014).

Streptozotocin (2-deoxy-2-(3-methyl-3-nitrosurea) 1-D-glucopyranose) is an antibiotic synthesized through the bacteria Streptomyces achromogenes and nitrosourea analogs (combined N-methyl-N-nitrosourea with carbon-2 from hexose) that are often used to induce experimental animals into diabetes mellitus (Ghasemi et

al., 2014). Streptozotocin is toxic to β-pancreatic cells because it can decrease the sensitivity of preferred insulin receptors, resulting in increased insulin resistance and blood glucose levels (Firdaus et al., 2016). Nicotinamide is a vitamin B, (niacin) derivate with an antioxidant capacity that reduces the cytotoxic actions of Streptozotocin. Nicotinamide works by stimulating regeneration in pancreatic beta cells and the growth of Langerhans islet cells and can block apoptosis reactions (Ghasemi et al., 2014). The combination of streptozotocin-nicotinamide administration can prevent excessive hyperglycemia and mortality in white rats. Nicotinamide administration before streptozotocin injection can protect pancreatic beta cells from toxic effects (Husan et al., 2019).

Based on the results of measuring rat blood glucose levels on day 18, the average blood glucose levels of rats in the Na-CMC 0.5%, glibenclamide, and the ethanol-water fraction of the longjack root ranged from 123.55 – 283.45 mg/dl. Na-CMC 0.5% does not have antidiabetic activity. Because Na-CMC is neutral, the Na-CMC solution is not effective enough in inducing antidiabetic activity characterized by a decrease in blood glucose levels (Panjaitan & Novitasari, 2021). In contrast, the glibenclamide treatment group and the ethanol-water fraction of longjack root obtained glucose levels of 124.26 mg/dL and 123.55 mg/dL.

Malondialdehyde is a stable end-result substrate of lipid peroxidation produced from interactions with free radicals in phospholipid membranes that become oxidative stress in people with type 2 diabetes and are found in red blood cell membranes (Solfaine et al., 2019). Based on the results of measuring MDA levels in Table 1, it can be seen that the MDA levels of the entire experimental rat group ranged from 1.71 – 9.66 nmol/ml. It shows that the MDA levels in experimental animals in the normal control group were within normal limits and had the lowest malondialdehyde levels compared to other groups of 1.71 nmol/ml. The Na-CMC 0.5% administration group showed an increase in blood glucose levels combined with the highest malondialdehyde levels of 9.66 nmol/mL. According to a previous study, Na-CMC does not have potential compounds that can lower blood glucose and MDA levels (Panjaitan & Astuti, 2021). The glibenclamide administration group showed a decrease in glucose and MDA levels by 3.02 nmol/ml. Glibenclamide has been reported to stimulate the release of insulin so that it can lower glucose levels in the blood (Gregory et al., 2019). The group of the ethanol-water fraction of longjack root showed a decrease in glucose levels and MDA levels of 2.83 nmol/ml.

The pancreas is an essential glandular organ in the body consisting of exocrine and endocrine tissues. The pancreatic endocrine consists of the Langerhans islet, which produces the hormone insulin, which will be secreted to break down the glucose in the blood (Oktavia et al., 2020). Based on the histopathological analysis of the pancreatic organs, the experimental animal group on normal control showed a normal condition of Langerhans islet structure. It is characterized by a monomorphic shape of Langerhans islet cells with a rounded cell nucleus, no degenerated cells, and necrosis cells. According to a previous study, the characteristics of normal pancreatic tissue are characterized by having a very dense cell nucleus, no swelling cells, and no necrosis cells (Pramesti & Widjanarko, 2014).

The group of experimental rats on negative control showed that the Langerhans islet was damaged. It is characterized by cells undergoing necrosis, hydropic degeneration characterized by a visible enlargement of the cell nucleus and nucleolus, fading boundaries between cells, and accumulation of water in the cytoplasm. Pancreas organ damage is characterized by changes in the shape of the pancreas in the form of shrinkage and reduction in size from the Langerhans islet, vacuolization of the cytoplasm, cells undergoing hydropic degeneration and necrosis (Miniawy et al., 2017; Nuralifah et al., 2022). The damage to pancreatic cells can be caused by various factors. Such factors include genetic factors, germs infection, diabetogenic substances, and free radicals (Khairani et al., 2018). The damage to Langerhans islet cells will cause a decrease in insulin production, causing hyperglycemia. Based on the results of the histopathological analysis obtained, the damage to Langerhans island cells is caused by the administration of STZ-NA. Streptozotocin causes the formation of highly reactive free radicals which cause damage to cell membranes, proteins, and DNA, thereby reducing insulin production by pancreatic beta cells (Ghasemi et al., 2014). STZ enters pancreatic beta cells through a glucose-2 transporter (GLUT2) which causes DNA alkylation by limiting the formation of ATP in mitochondria, increasing enzyme xanthine oxidase, and inhibiting the Krebs cycle (Firdaus et al., 2016; Panjaitan & Novitasari, 2021).

In the positive control group, the condition of the islets of the Langerhans structure improved. It is shown by the pancreatic islets of Langerhans cells which appear monomorphic, have round nuclei, and have dense chromatin. Some cells degenerate with blurred intercellular boundaries, cytoplasmic vacuolization, and cell necrosis. Glibenclamide is an oral hypoglycemic sulfonylurea derivate that reduces blood glucose levels, increases insulin secretion, and repairs pancreatic beta cells (Walean et al., 2020). According to a previous study, glibenclamide's mechanism is inhibiting ATP-sensitive potassium channels in pancreatic β-cells. This inhibitory mechanism can cause depolarization of the cell membrane, which can generate voltage so that the

calcium channels open. The cell membrane depolarizes and opens voltage-dependent calcium channels so Ca 2+ can enter the cytosol and increase intracellular calcium in pancreatic beta cells, which ultimately stimulates the release of insulin and repairs pancreatic beta cells. (Walean et al., 2020).

The ethanol-water fraction group showed an improvement in a pancreatic structure characterized by a monomorphic cell shape, few degenerated cells were found, and no necrotic cells were found. Longjack root is reported to contain various chemical compounds that act as antioxidants, such as quassinoids, flavonoids, triterpenoids, saponins, carotenoids, and alkaloids. In addition, most of the chemical compounds in longjack roots are quassinoids (Mohamed et al., 2015). In addition, most of the chemical compounds in longjack roots are quassinoids. According to a previous study, quassinoids in longjack roots have activity as hepatoprotective with their mechanisms as antioxidants so they can protect liver cells (Panjaitan et al., 2013). Not only that, quassinoid compounds play a role in repairing lipid peroxidation to prevent necrosis (Shiyamita et al., 2013). Flavonoids can reduce blood sugar by inhibiting the action of the enzyme α-glucosidase which has the function of hydrolyzing oligosaccharides into monosaccharides. (Iryani et al., 2017). Triterpenoids can reduce blood glucose levels in STZ-induced rats by increasing insulin secretion from the pancreas. Saponins can increase insulin secretion in pancreatic β cells (Zakaria, 2019).

Conclusion

The ethanol-water fraction of longjack root at a dose of 500 mg/kg body weight has an antidiabetic activity characterized by a decrease in glucose levels, MDA levels, and repair of the structure of the pancreas of white rats damaged by STZ-NA.

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Author Contributions
Wiwik Hartika prepared proposals, final reports, and article manuscripts. Michelle Terence carried out the preparation of proposals, progress reports, research preparations, preparation of the activity and financial logbooks, and preparation of the final report. Ikhsan Samir prepared the proposal, research preparation, preparation of the final report. Ruqiah Ganda Putri Panjaitan conducted thorough research starting from preparing proposals, research design, research preparation, preparation of activity and financial logbooks, preparation of progress reports, preparation of final reports, and preparation of article manuscripts.

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Conflicts of Interest
The authors declare no conflict of interest.

References

Arief, H., & Widodo, M. A. (2018). Peranan Stress Oksidatif pada Proses Penyembuhan Luka. *Jurnal Ilmu Kedokteran Wijaya Kusuma,* 5(2), 22-29. http://dx.doi.org/10.30742/jikw.v5i2.338

Dompeipen, E. J., & Simanjuntak. (2015)Aktivitas Antidiabetes dan Antioksidan Kapang Endofit dari Tanaman Mahoni (*Swietenia macrophylla* King.). *Biopropal Industri,* 6(1), 7-17. http://dx.doi.org/10.36974/jbi.v6i1

Fatimah, R. N. (2015). Diabetes Mellitus Tipe 2. *Jurnal Majority,* 4(5), 93-101. Retrieved from https://juke.kedokteran.unila.ac.id/index.php/majority/article/view/615/619

Firdaus, Rimbawan, Maliyati, S. A., & Roosita, K. (2016). Model Tikus Diabetes yang Diinduksi Streptozotocin-Sukrosa untuk Pendekatan Penelitian Diabetes Mellitus Gestational. *Jurnal MKMI,* 12(1), 29-34. https://doi.org/10.30597/mkmi.v12i1.550

Fransisca, Kalangi, G. E., Saptasari, D.C., & Hendra, P. (2018). The Effect of Pasak Bumi Roots Towards Blood Glucose Level in Glucose Loaded-Mice. *Jurnal Farmasi Sains dan Komunitas,* 15(1), 1-6. https://doi.org/10.24071/jpsc.00965

Gashemi, A., Khalifi, S., & Jedi, S. (2014). Streptozotocin-Nicotinamide-Induced Rat Model of Type 2 Diabetes (Review). *Acta Physiologica Hungarica,* 101(4), 408-420. https://doi.org/10.1556/APhysiol.101.2014.4.2

Gregory, M. M., Sung, M. W., Yang, Z., Innes, L. M., Kandasamy, B., David, L., Yoshioka, C., & Shyng, S. L. (2019). Mechanism of pharmacy chaperoning in a mammalian KATP channel revealed by cryo-EM. *Journal Elife,* 1(1), 1-26. https://doi.org/10.7554/eLife.46417

Hazni, R., Gustiawan, R., Zulfian, Lestari, S. M. P., Arania, R., & Sudiadnyani, N. P. (2021). Penyuluhan Diabetes Mellitus di Puskesmas Rawat Inap Sukaraja Bandar Lampung. *Jurnal Kreativitas Pengabidan Kepada Masyarakat* 4(1), 181-187. http://doi.org/10.33024/jkpm.v4i1.3728

Hidayati, S., Zuhud, E. A. M., Adiyaksa, I. K., & Manar, P. A. (2021). Review: Etnotaksonomi dan Bioteknologi Tumbuhan Pasak Bumi (*Eurycoma*

longifolia Jack.). *J of Natural Resources and Environmental Management* 11(2), 177-188. http://dx.doi.org/10.29244/jpsl.11.2.177-188

Husan, 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

IDF Diabetes Atlas. (2021) *International Diabetes Federation (IDF), 10th Edition.* Brussels: International Diabetes Federation. Retrieved from https://diabetesatlas.org/

Iryani, I., Iswendi, I., & Katrina, I. T. (2017). Uji Aktivitas Antidiabetes Mellitus Senyawa Metabolit Sekunder Fraksi Air dari Beras Ketan Hitam (*Oryza satival. Var glutinosa*) pada Mencit Putih. *Eksakta,* 18(1), 54-60. https://doi.org/10.24036/eksakta/vol18-iss01/17

Jurnalis, Y. D., Sayoeti, Y., & Elfitrimelly, E. (2014). Peran Antioksidan pada non Alcoholic Fatty Liver Disease (NAFLD). *Jurnal Kesehatan Andalas,* 3(1), 15-20. https://doi.org/10.25077/jka.v3i1.18

Khairani, Yuniarti, E., & Sumarmin, R. (2018). Pengaruh Ekstrak Kulit Buah Manggis (*Garcinia mangostana* L.) terhadap Histopatologi Pankreas Mencit (*Mus musculus* L. Swiss Webster) yang Diinduksi Sukrosa. *Eksakta,* 19(1), 100-112. https://doi.org/10.24036/eksakta/vol19-iss1/123

Khajinou, T., & Jiraungkoorskul, W. (2016). Review The Ergogenic Effect of Long Jack (*Eurycoma longifolia*). *Pharmacognosy Rev* 10(20), 139-141. http://doi.org/10.4103/0973-7847.194041

Liem, S., Yuliet, & Khumaidi, A. (2015). Uji Aktivitas Antidiabetes Kombinasi Glibenklamid Dan Ekstrak Daun Salam (*Syzygium Polyanthum* Wight.) Terhadap Mencit (*Mus Musculus*) Yang Diinduksi Aloksan. *Galenika Journal of Pharmacy,* 1(1), 42-47. https://doi.org/10.22487/j24428744.2015.v1.i1.4831

Miniawy, H. M. F. E. L., Ahmed, K.A., Ibrahem, E. M., Sabry, D., Tahany, A., Ismail, & Amer, E. (2017). Camel's Wharton Jelly Mesenchymal Stem Cell is a Novel Tool for Regeneration of Induced Diabetes Mellitus. *Journal of Translational Science,* 3(5), 1-6. http://doi.org/10.15761/JTS.1000196

Mohamed, A. N., Vejayan, J., & Yusoff, M. M. (2015). Review on *Eurycoma longifolia* Pharmacological and Phytochemical Properties. *Journal of Applied Sciences*, 15(6), 1-14. http://doi.org./10.3923/jas.2015.831.844.

Nuralifah, Fitrawan, L. O. M., Parawansah, & Trisetya M. (2022). Histopatologi Organ Pankreas Tikus DM tipe 2 yang diberi Ekstrak Daun Gedi Merah (*Abelmoscus manihot* L. Medik). *Journal Syifa Sci and Clinical Research,* 4(1), 141-151. https://doi.org/10.37311/jsscr.v4i1.13566

Oktavia, F., Erianto, M., & (2020). Pola Penderita Karsinoma Pankreas di RSUD Dr. H. Abdul Moeloek. *Jurnal Ilmiah Kesehtan Sandi Husada*, 9(2), 741-747. https://doi.org/10.35816/jiskh.v12i2.393

Panjaitan, R. G. P., & Astuti, A. (2021). Antidiabetic Activity of The Leaf Extract of *Eurycoma longifolia* Jack. in Streptozotocin-Nicotinamide Induced Diabetic Model. *Pharmacogn Journal,* 13(6), 1582-1588. http://doi.org/10.5530/pj.2021.13.203.

Panjaitan, R. G. P., Handharyani, E., Zakiah Z, Manalu W. 2013. Hepatoprotective Activity of *Eurycoma longifolia* Jack. Roots. *Indian J of Traditional Knowledge*, 12(2), 225-230. Retrieved from https://nopr.niscpr.res.in/handle/123456789/16865

Panjaitan, R. G. P., & Novitasari. (2021). Anti-diabetic Activity of the Red Dragon Fruit Peel (*Hylocereus polyrhizus*) in Ethanol Extract Againts Diabetic Rats. *Pharmacognosy Journal,* 13(5), 1079-1085. http://doi.org/10.5530/pj.2021.13.140

Prakosa, A. G., Ratnawati, R., & Prabawati, R. K. (2017). Pengaruh Antosianin Ungu (*Ipomoea batatas* L.) Kultivar Gunung Kawi terhadap Ekspresi Caspase-3 pada Jaringan Otak Tikus Model DM Tipe 2. *Majalah Kesehatan,* 4(2), 52-58. https://doi.org/10.21776/ub.majalahkesehatan.2017.004.02.1

Puspitasari, S., & Syauqy, A. (2015). Pengaruh Pemberian Pisang Kepok (*Musa paradisiaca Forma Typical*) terhadap Kadar Malondialdehid (MDA) Tikus Sprague Dawley Pra-Sindrom Metabolik. *Journal of Nutrition College,* 4(2), 314-322. https://doi.org/10.14710/jnc.v4i4.10101

Putri, E. P., Gofur, A., & Lestari, S. R. (2017). Pengaruh Variasi Campuran Ekstrak Tempe Kedelai Hitam dan Ubi Jalar Ungu terhadap Aktivitas Lipid Perozidation dan Reactive Oxygen Species (ROS) Total pada Tikus Model Diabetes Mellitus Tipe 2. *Jurnal Ilmu Hayat*i, 1(2), 76-85. http://dx.doi.org/10.17977/um061v1i22017p76-85

Rantung, J., Yetti K., & Herawati, T. (2015). Hubungan Self-Care dengan Kualitas Hidup Pasien Diabetes Mellitus (DM) di Persatuan Diabetes Indonesia (PERSADIA) Cabang Cimahi. *Jurnal Skolastik Keperawatan,* 1(1), 38-51. https://doi.org/10.35974/jsk.v1i01.17

Solfaine, R., Muniroh, L., & Mubarokah, W. W. (2019). Efek Ekstrak Daun *Tithonia diversifolia* terhadap Penurunan Konsentrasi Adiponektin pada Tikus Diabetik yang Diinduksi oleh Streptozotocin. *Jurnal Sains Veteriner,* 37(2), 143-150. https://doi.org/10.22146/jsv.46837

Suastuti, N. G.A M. D.A., Dewi, I. G. A. K. S. P., & Ariati, N. K. (2015). Pemberian Ekstrak Daun Sirsak

(*Annona muricuta*) untuk Memperbaiki Kerusakan Sel Beta Pankreas Melalui Kadar Glukosa Darah, Advanced Glycation, and Product, dan 8-hidroksi-2-dioksiguanosin pada Tikus Wistar Hiperglikemia. *Jurnal Kimia* 9(2), 289-295. https://doi.org/10.24843/JCHEM.2015.v09.i02.p21

Suryani, N., Endang, T., & Aulanni'am. (2014). Pengaruh Ekstrak Metanol Biji Mahoni terhadap Peningkatan Kadar Insulin, Penurunan Ekspresi TNF-α dan Perbaikan Jaringan Pankreas Tikus Diabetes. *Jurnal Kedokteran Brawijaya,* 27(3), 137-145. https://doi.org/10.21776/ub.jkb.2013.027.03.3

Verma, S., Gupta, M., Popli, H., & Aggarwali, G. (2018). Diabetes Mellitus Treatment Using Herbal Drugs. *International Journal of Phytomedicine,* 10(1), 1-10. http://doi.org/10.5138/09750185.2181

Walean, M., Melpin. R., Rondonuwu. M., & Pinontoan, K. F. (2020). Perbaikan Histopatologi Pankreas Tikus Hiperglikemia setelah Pemberian Ekstrak Etanol Kulit Batang Pakoba (*Syzygium luzonense* (Merr.) Merr.). *Majalah Ilmiah Biologi Biosfera: A Scientific Journal,* 37(1), 43-48. http://doi.org/10.20884/1mib.2020.37.1.1210

Wiendarlina, I. Y., Rahminiwati, M., & Gumelar, F. T. (2018). Aktivitas Hepatoprotektor Ekstrak Air Herba Pegagan Daun Kecil (*Centella asiatica* L. Urb.) terhadap Tikus Putih Jantan *Sprague Dawley* L. yang Diinduksi dengan Parasetamol. Fitofarmaka. *Jurnal Ilmiah Farmasi,* 8(1), 13-24. http://doi.org/10.33751/jf.v8i1.1167

Zakaria, A., Yahya, Z., & Nurmayunita, H. (2019). Pengaruh Pemberian The Daun Tin terhadap Kadar Gula Darah pada Penderita Diabetes Mellitus. *Jurnal Ilmu Kesehatan,* 7(2), 357-365. https://doi.org/10.32831/jik.v7i2.215