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Effectiveness of inai leaf extract (*Lawsoniainermis*Linn) and noni fruit extract (*Morindacitrifolia*L.) as antihiperglicemic on rats inducted by aloxan

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Abstract: *One of the ways to handle of hyperglycemia cases is by developing herbal medicines. In this case, research has been carried out on "the effectiveness of inai leaf extract (Lawsoniainermis Linn) and noni fruit extract (Morindacitrifolia L.) asantihyperglycemic against to rats was induced alloxan".The study used a laboratory experimental method and a completely randomized design (CRD) with a normal control group (physiological saline), a control group that was treated with alloxan (150 mg/kg, peritoneal injection/i.p), alloxan group (150 mg/ kg.ip)+standard drug (metformin) (5 mg/kg, po), alloxan group (150 mg/kg.ip)+henna and noni extract (1:2 = 125:800 mg/kg body weight), alloxangroup+henna extract and noni (1:1 = 125:400 mg/kg body weight), alloxangroup+henna extract and noni (2:1 = 250:400 mg/kg body weight). Observations were carried out every three days from days to 0, 3, 6, 9, 12, and 15 for each test parameter such as rat weight, blood sugar level, and diameter of the pancreatic Langerhans island.The results showed that metformin effectively as antihyperglycemic and was not different significantly with the extract combination of henna leaf extract (L. inermis Linn) and noni (M. citrifolia L.).It was concluded that the combination of henna leaf extract (L. inermis Linn) and noni fruit extract (M. citrifolia L.) had antihyperglycemic effectiveness against to rats was induced alloxan.***

Key Word*: Lawsoniainermis Linn, Morindacitrifolia L., and antihyperglycemic*

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I. Introduction

The term "hyperglycemia" comes from the Greek hyper (high) + glykys (sweet / sugar) + haima (blood). Hyperglycemia is blood glucose greater than 125 mg/dL when fasting and greater than 180 mg/dL 2 hours postprandial. A patient experiences impaired glucose tolerance, or pre-diabetes, with fasting plasma glucose 100 mg/dL up to 125 mg/dL. A patient is called diabetes with fasting blood glucose greater than 125 mg/dL [1]

Diabetes has become a global issue and is included in the Non-Communicable Disease (PTM) group. Ninety to ninety-five percent of Diabetes is a type 2 diabetes. Prevention can be done by changing lifestyles that are not in favor of health. The greatest threat to the Indonesian nation against Diabetes has been on the verge of being proven and Indonesia is the sixth country of diabetics after several other countries in the world, namely 10.3 million people (aged 20-79 years). show the report of survey results from Basic Health Research (Riskesdas) with the high prevalence of Diabetes, which is 6.9% in 2013 increased to 8.5% in 2018. This figure can give an estimate of the number of people with diabetes reaching sixteen million people and allegedly can cause heart disease, the incidence of strokes, disturbances and kidney disorders and cause motor problems can even cause death [2].

Although antidiabetic or antihyperglycemic drugs have been widely available in the market and are quite effective, herbal medicines are quite popular and are used by the community because the prices are quite cheap and have side effects that are not too worrying [3]. Some antihyperglycemia research that has been studied is SaurauiavulcaniKorth [4], danLawsoniainnermis [5][6][6], *M. citrifolia* L. [7].

It has been reported that the administration of herbal medicines in the form of concoctions or a combination of several medicinal plants. The use of medicinal herbs, in combination form is considered a type of combination therapy due to the complexity of phytochemicals and bioactivity in plants. Thus, herbal concoctions containing thousands of phytochemicals have many benefits by targeting several cell metabolic pathways. It has been proven that the combination therapy of herbal medicines together is better than mono herbs [8].

II. Material And Methods

Experimental Animals

Adult male white rats obtained from Biology, Faculty of Mathematics and Natural Sciences, University of North Sumatra. Wistar rats (Rattusnorvegicus) weigh about 150-200 grams, age 8-11 weeks and total 30 rats.

Research design

The study was conducted using a completely randomized design (CRD) of six treatments and five replications as follows; Noni extract 125 mg/kg BW [7]. While ethanolic extract of leaves (*L. inermis* Linn.) Was 400 mg/kg BW of rats (Rattusnorvegicus). G0: Solvent control (physiological saline), G1: Alloxan (150 mg/kg.ip), G2: Alloxan + Metformin (5 mg/kg, po), G3: Alloxan + Inlant and Noni Extract (1: 2 = 125:800 mg/kg BW), G4: Alloxan + Ini and Noni Extract (1:1 = 125:400 mg/kg BW), G5: Alloxan + Ini and Noni Extract (2:1 = 250: 400 mg/kg BW). Group G0: Normal control (physiological salts). Group G1: Control treated with Aloxane (150 mg/kg, peritoneal injection / i.p). Group G2: Alloxan (150 mg/kg.ip) + Standard drug (Metformin) (5 mg/kg, po), Group G3: Aloxan (150 mg/kg.ip) + Inai and Noni Extract (1: 2 = 125 : 800 mg/kg BW, Group G4: Alloxan + Inai and Noni Extract (1:1 = 125:400 mg/kg BW), Group G5: Alloxan + Inai and Noni Extract (2:1 = 250: 400 mg/kg body weight).

Inai leaf extract, noni fruit, metformin standard drug (5 mg/kg) and physiological salt are given with the help of a gavage needle. The G0 group functioned as normal controls, who received physiological saline (0.9%) for 15 days. Group G2 to Group G5 were diabetic control rats who had previously received alloxan, given hyacinth extract at a dose of 125 mg/kg, po and noni 400 mg/kg, po, and the standard drug metformin (5 mg/kgBB) for 15 consecutive days

Number of Research Samples

amples of male rats totaled 25 tails based on the calculation of the Federer formula (1963), namely; (t-1) (n-1) ≥15, t = treatments, n = replication of each group. If the number of research groups is five, then the number n = 5, but in the implementation and to maintain the presence of rats, one mouse is added per group so that the number of samples in the laboratory is 30.

Phytochemical Profile

Phytochemical profile is done by checking the extract from the leaves of inai and noni fruit with; tannin, alkaloid, flavonoid, phenol, steroid / triterpenoid, terpenoid, and saponin tests.

Measurement of blood sugar levels

During the 16 (sixteen) hours of rats to be examined fasting occurs before glucose levels are measured [9]. The measurement uses the GlukoDrTM Blood Glucose Test Meter from the blood of the tip of the rat's tail. Then drop on the GlukoDrTM test strip. Wait until about eleven seconds to be able to read the numbers listed on the device in mg/dL units.

Making of Pancreatic Preparations

At the end of the treatment, pancreatic preparations were made with haematoxylin eosin staining. Langerhans Island was observed with a magnification of 10x10 [10].

Data analysis

The collected data were analyzed by ANOVA at the 5% level boosted and when $p < 0.05$, it was continued with the Post Hoc Test - Duncan test to compare between treatment groups.

III. Result

Based on the results of research conducted at the Animal House Biology Laboratory of the Faculty of Mathematics and Natural Sciences, University of North Sumatra, the Pharmacology Laboratory of the USU Faculty of Pharmacy, and the Clinical Pathology Laboratory of the Haji Adam Malik Hospital in Medan, several test parameters can be reported in several Tables and Figures in below this.

Phytochemical Results

From the results of phytochemical observations of each leaf of henna (*Lawsoniainnermis* Linn.) And Noni fruit (*M. citrifolia* L.) obtained reports as in Table 1. the following.

Table no 1: Profile of phytochemical content of ethanol extract of *Lawsoniainermis* Linn. leaves and*M. citrifolia* fruit

No.	Compounds	*L. inermis* (Linn)	*M. citrifolia*
1.	Flavonoids	+	+
2.	Tannin	+	+
3.	Alkaloids	+	+
4.	Phenol	+	+
5.	Steroids	-	+
6.	Terpenoids	-	+

Note: G0: Negative Control (No Treatment), G1: Positive Control (Alloxan-induced treatment only), G2: Metformin, G3: Inai Extract: Noni (1: 2), G4: Inai Extract: Noni (1:1), and G5: Inai Extract: Noni (2:1).

Body Weight of Rats

Rats weighed before and after injection of alloxan were recorded and arranged in Table 2.

Table no2: Average body weight of rats (g) before and after alloxan injection.

No.	Groups	Before	After	*pvalue*(before and after)
1	G0	221.33±29.74	223.33±26.58	0.695
2	G1	195.33±35.44	188.33±31.21	
3	G2	232.00±22.12	223.33±22.55	
4	G3	178.67±22.05	173.67±23.03	
5	G4	186.33±12.50	182.67±12.50	
6	G5	208.00±13.11	203.00±13.11	

Average body weight of rats was observed every three days of the study tour until the end of the study (fifteen days). The results are written in Table 3 and Figure 3 below.

Table no 3: Average body weight of rats (g) on several days of observation until the end of thetreatment.

No.	P	Hari					
		0	3	6	9	12	15
1	G0	221.67±28.68$^{bcde}_{fghi}$	231.00±23.26$_{ghi}$	235.33±23.80$_{hi}$	241.00±23.64$_{hi}$	245.33±23.18$_{hi}$	250.67±23.35$_{i}$
2	G1	192.00±33.05$^{abcd}_{efg}$	185.33±30.29$^{abcd}_{ef}$	184.00±30.81$_{abcdef}$	183.00±31.00$_{abcde}$	180.67±30.44$_{abc}$	179.67±30.44$_{ab}$
3	G2	226.00±22.65$_{fghi}$	220.00±22.07$^{bcde}_{fghi}$	223.00 ±21.52^{defghi}	222.00±21.52$^{cdef}_{ghi}$	224.67±21.03$_{efghi}$	225.33±20.50$_{fghi}$
4	G3	176.00±21.93$_{a}$	170.33±22.81$_{a}$	174.33±23.46$_{a}$	175.00±24.27$_{a}$	176.33±26.08$_{a}$	177.00±24.56$_{a}$
5	G4	185.33±13.50$^{abcd}_{ef}$	173.33±7.09$_{a}$	176.33±7.57$_{a}$	177.00±6.93$_{a}$	179.67±7.23$_{ab}$	181.00±7.81$_{abcd}$
6	G5	205.67±13.20$^{abcd}_{efgh}$	186.67±1.53$_{abcdef}$	189.33±0.58$^{abcdef}_{g}$	191.00±1.00$^{abcdef}_{g}$	193.33±0.58$^{abcdef}_{g}$	191.67±5.86$^{abcdef}_{g}$

Note: P: Treatment group. G0: Negative Control (Without Treatment), G1: Positive Control (Alloxan-induced treatment only), G2: Metformin, G3: Inai Extract: Noni (1: 2), G4: Inai Extract: Noni (1:1), and G5 :Inai Extract: Noni (2:1). $p^{a,b,c,d,e,f,g,h,i}<0.05$ or unequal lowercase notation in the same / different column and / or column is significantly different at the 5% error level.

To see in full the results of observations of body weight of wistar rats in animal hosue can be considered Figure 1.

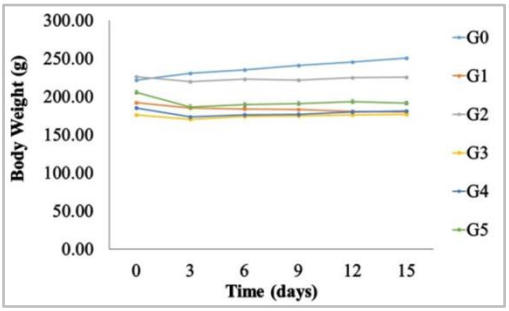

Fig1: Average body weight of rats (g) on several days of observation during the study. Note: G0: Negative Control (Without Treatment), G1: Positive Control (Alloxan-induced treatment only), G2: Metformin, G3: Inai Extract: Noni (1: 2), G4: Inai Extract: Noni (1:1), and G5: Inai Extract: Noni (2:1).

Blood sugar levels

The results of measurements of rat blood sugar levels before and after injection of alloxan are listed in the following Table 4.

Table no 4: Average blood sugar levels (mg/dL) of rats before and after injection of alloxan in several treatment groups.

No.	Groups	Before	after	% se of increasing
1	G0	112.00±12.17	113.00±13.89	0.89
2	G1	197.67±71.43	405.00±49.79	104.89
3	G2	262.33±183.71	371.00±185.45	41.42
4	G3	213.67±107.16	357.67±211.97	67.39
5	G4	121.67±12.22	252.00±55.22	107.12
6	G5	129.00±4.58	377.33±151.05	192.51

Blood sugar levels in rats in Table 5 appear to vary and generally from day to day there is a decrease in blood sugar levels in each treatment giving a combination of henna extract and noni.

Table no 5: Average blood sugar levels of rats (mg/dL) on several days of observation until the end of the treatment.

No.	P	Days					
		0	3	6	9	12	15
1	G0	113.00±13.89 ab	112.67±11.85 ab	115.67±11.93 ab	113.33±13.43 ab	114.33±9.87 ab	104.33±8.33 a
2	G1	405.00±49.79 ij	375.67±45.96 ij	362.00±45.53 hij	357.67±41.02 hij	341.67±46.23 ghij	294.33±8.33 efghij
3	G2	371.00±185.45 ij	409.00±143.68 j	304.00±168.60 efghij	267.00±111.34 abcdefghij	183.67±35.35 abcdefg	142.67±10.60 abcde
4	G3	357.67±211.97 hij	331.33±121.46 fghij	291.33±94.88 defghij	275.67±97.60 bcdefghij	188.00±53.36 abcdefg	132.33±11.59 abcd
5	G4	252.00±55.22 abcdefghij	243.00±51.22 abcdefghi	203.33±16.50 abcdefgh	177.00±14.42 abcdef	127.67±32.35 abc	111.33±15.70 a
6	G5	377.33±151.05 ij	327.67±98. fghij	285.00±83.36 cdefghij	249.33±52.27 abcdefghij	200.33±26.84 abcdefgh	161.00±1.73 abcde

Note: P: Treatment group. G0: Negative Control (Without Treatment), G1: Positive Control (Alloxan-induced treatment only), G2: Metformin, G3: Inai Extract: Noni (1: 2), G4: Inai Extract: Noni (1:1), and G5 :Inai Extract: Noni (2:1). Data analysis: $p^{a,b,c,d,e,f,g,h,i}$<0.05 or unequal lowercase notation in the same / different column and / or column is significantly different at the 5% error level.

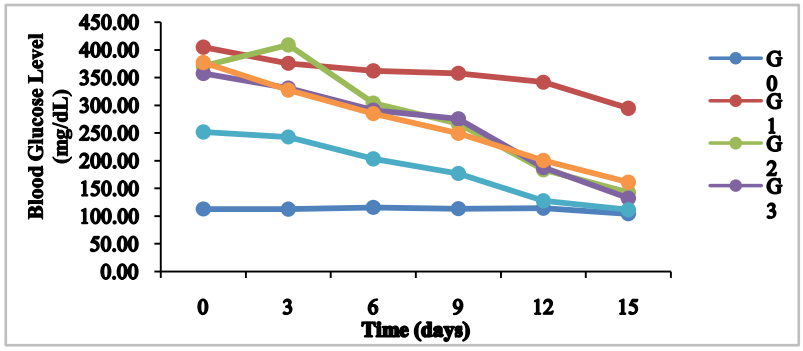

Fig 2. Average blood sugar levels (mg/dL) on several days of observation during the study. Note: G0: Negative Control (Without Treatment), G1: Positive Control (Alloxan-induced treatment only), G2: Metformin, G3: Inai Extract: Noni (1: 2), G4: Inai Extract: Noni (1:1), and G5: Inai Extract: Noni (2:1).

The Area of Langerhans Island Pancreas

In Figure 3 there are differences in the area of the Langerhans islands between the various treatments in studies conducted on hyperglycemic rats. Langerhans Island is associated with the presence of β cells which function to produce insulin to degenerate blood glucose. B cells account for 70% of the islets of Langerhans which means that the size of the islets of Langerhans is largely determined by the presence of β cells.

Figure 3. Average area of Langerhans Island (µm2) on several days of observation during the study. Note: G0: Negative Control (Without Treatment), G1: Positive Control (Alloxan-induced treatment only), G2: Metformin, G3: Inai Extract: Noni (1: 2), G4: Inai Extract: Noni (1:1), and G5: Inai Extract: Noni (2:1).

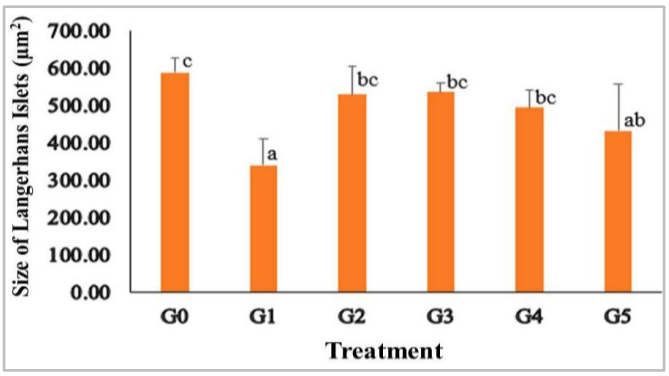

Fig 3. Average area of Langerhans Island (µm2) on several days of observation during the study. Note: G0: Negative Control (Without Treatment), G1: Positive Control (Alloxan-induced treatment only), G2: Metformin, G3: Inai Extract: Noni (1: 2), G4: Inai Extract: Noni (1:1), and G5: Inai Extract: Noni (2:1).

IV. Discussion

The content of the ethanol extract of the leaves of *L. inermis* (Linn) and *M. citrifolia* fruits which were examined qualitatively were four successive compounds (flavonoids, tannins, alkaloids, and phenols) and six compounds (flavonoids, tannins, alkaloids, phenols, respectively steroids and terpenoids). In accordance with research, that the ethanol extract of *Lawsoniainermis* (Linn) leaves are flavonoids, tannins, alkaloids, and phenols [11]. Hasilpenelitianlain, ekstraketanol*L. inermis* (Linn) while other studies also found *M. citrifolia* contents including flavonoids, tannins, alkaloids, phenols, steroids, and terpenoids [12]. (10)

In the Table 2 it can be seen that the results of a comparison analysis of body weight of rats before and after administration of alloxan were not significantly different ($p > 0.05$). This proves that there is no effect of alloxan injection on changes in body weight of rats. Aloxan can increase rat blood sugar levels but is not directly related to changes in body weight of rats. This is likely due to the injection of alloxan or an increase in acute sugar levels so that the metabolic process has not yet fully occurred which causes weight gain. Body weight measurements carried out two days after the increase in blood sugar levels, so that it does not affect the change in body weight of rats. Although in the research report there is a significant relationship increase in blood sugar levels to weight gain. As the researcher statement, that body weight marked by body mass index (BMI) is positively correlated with blood sugar levels or Fast Blood Glucose (FBG) so that increased KGD is at risk for obesity according to certain situations and conditions [13]. But according to other researchers, that lower body weight or BMI can be associated with increased glycemic variability, characterized by increased PPGEs (postprandial glucose excursions / blood sugar levels after meals) in newly diagnosed type 2 diabetes patients [14].

In Table 3 it can be seen that the mean body weight of rats is significantly different ($p < 0.05$) when compared to all the average body weight of rats in all observations starting from observations from the first day until the fifteenth day. Rats' body weight tended to increase until the end of the study (G0 and G3), although more decreased (G1, G2, G4, and G5). But the increase and decrease in body weight of these rats did not differ significantly when compared to the initial and final body weight of the study. This shows that the rats were healthy during the study and also their weight was not affected by changes in blood sugar levels during the study. Like the results of other studies, that a simple and non-invasive method for assessing the health and well-being of rats for clinical evaluation of rats in biomedical research is the Body condition score (BCS) technique, namely body weight condition. This method can be a sensitive objective assessment such as weight loss in animal models where organ enlargement, ascites (increased body fluids), or tumor development can be monitored by weight loss. Although the deposition of fat is similar in mice and rats, namely rats. For example in other studies there is a positive correlation between BCS scores and kidney function and a negative correlation between weight and kidney function. These results support the use of BCS as an effective and non-invasive health assessment method in this mouse model [15].

In Figure 1 it can be concluded that there is a tendency for changes in rat weight during the study. But in outline the changes seen for each treatment were not significant ($p > 0.05$; Table 2). Weight loss was seen more at the third day of observation and then it stabilized at at sixth day until the end treatment.

Table 4 shows the blood sugar levels of rats that were ready for research, especially on sugar levels after alloxan injection. This is done to ensure an increase in blood sugar so that rats have experienced an increase in blood sugar levels and can be continued in research treatment measures. After conducting research with various treatments, the results obtained as in Table 4 and Figure 2.

Rat blood sugar levels that increase after administration of alloxan have reached levels that indicate the condition of hyperglycemia or diabetes. An increase in sugar levels from 252.00 ± 55.22 - 405.00 ± 49.79 mg/dL or up from 41.42-192.51% in alloxan injections. This has passed the diabetes standard in rats of> 200 mg/dL. As stated by other researchers, rats have reached diabetes standards after reaching> 200 mg/dL[16]. According to other researchers, that alloxan and streptozotocin are glucose toxic analogs which are preferably accumulated in pancreatic beta cells through the glucose transporter GLUT2 (Glucose transporter 2). In the presence of intracellular thiols, especially glutathione, alloxan produces Reactive Oxygen Species (ROS) in cyclic redox reactions with their reduction products, namely dialuric acid. Autoxidation of dialuric acid produces superoxide radicals, hydrogen peroxide and, in the final reaction step catalyzed by iron, the hydroxyl radical. These hydroxyl radicals are ultimately responsible for the death of beta cells, which have very low antioxidant defense capacity, and the subsequent state of 'insulin alloxan' which is insulin dependent. As a thiol reagent, alloxan also selectively inhibits glucose-induced insulin secretion through its ability to inhibit glucose cell glucocinase beta sensors [17].

Giving a combination of henna extract and Noni extract ratio of 1: 2, 1:1, and 2:1 seems to reduce blood sugar levels at the end of observation (day 15). The best decrease in blood sugar levels (significantly different ($p < 0.05$) was in G3 and G5, while G4 decreased blood sugar levels but was not significant ($p > 0.05$) when compared between the first day to day blood sugar levels Finally, between G3 and G5 in lowering blood sugar levels, G3 is slightly better than G5, which means that the ratio of ethanol extract levels of inai leaves: noni (1: 2) is better than the ratio of 1:1 and 2:1. Results of blood sugar levels obtained at the end of the observation did not differ significantly ($p > 0.05$) with the gold standard or standard drug patent (Metformin) that has been circulating for a long time.According to other studies, using ethanolic extract of single henna leaves have been able to reduced blood sugar levels of rats up to a dose of 400 mg/kgBB to 15.2% on day 14, and on day 28 had decreased by 41.3% [11].

Research results on phytochemical screening from the leaves of *Lawsonia inermis* (Linn) contained phenolic compounds such as coumarin, flavonoids, naphthalene and gallic acid derivatives, as well as glycosylation proteins. Flavonoid activity can reduce the activity of superoxide anions, peroxide radicals and hydroxy radicals by protecting the lipid membrane of pancreatic β cells against damaging oxidation reactions. In addition, administration of antioxidants can increase the mass of β cells of the pancreas so as to maintain the balance of insulin in it [18].

Noni fruit extracts can also reduce sugar levels through the saponin activity contained in the fruit. According to other studies, carrying saponins and flavonoids in *M. citrifolia* fruit can act as a trigger for increased insulin secretion. *M. citrifolia* fruit extracts show promising in vivo results as a natural antidiabetic agent. But scientists must pay attention to its safety, especially hearts. If the dose is adjusted within a safe range and proven efficacy, preclinical studies will be highly recommended [7].

Giving alloxan in the treatment of hyperglycemic mouse models causes β cell damage so that the production of insulin to degrade blood sugar decreases. As a result, rat blood sugar becomes increased. In accordance with other studies, that the influence of alloxan compounds can cause beta cell death by necrosis and cell degeneration [19]. Menuurut informasinya, bahwa 40-50% sel beta dapat mengalami nekrosis. Pada penelitian lain, dilaporkan bahwa inti sel β mengalami kariolisis, terjadinya disintegrasi pada bagian sitoplasma, tidak jelas batas-batas sel, serta ditemukan adanya masa debris berupa fragmen-fragmen inti (apoptosis) serta adanya nekrosis [20]. According to existing research, that cell apoptosis can be characterized by the presence of nuclear DNA fragmentation that occurs in cells (Situmorang et al., 2019; Situmorang & Ilyas, 2018b, 2018a, 2019) [25].

V. Conclusion

Based on the results and discussion of the research results that have been completed, the conclusions in detail can be conveyed as below; Inai leaf extract (*L. inermis* Linn) and noni fruit extract (*M. citrifolia* L.) haveantihyperglycemic effects in alloxan-induced rats. Metformin has an antihyperglycemic effect on alloxan-induced rats. The antihyperglycemic effect of inai leaf extract (*L. inermis*Linn) and noni (*M. citrifolia* L.) extract was not significantly different from metformin in alloxan-induced rats.

References

[1] M. Bashir, E. Naem, F. Taha, J. C. Konje, and A. Abou-samra, "Diabetes & Metabolic Syndrome : Clinical Research & Reviews Outcomes of type 1 diabetes mellitus in pregnancy ; effect of excessive gestational weight gain and hyperglycaemia on fetal growth," *Diabetes Metab. Syndr. Clin. Res. Rev.*, vol. 13, no. 1, pp. 84–88, 2019.

[2] N. A. W. Litta Marlin Patty, Jodelin Muninggar, "Profile of Lungs Volume In The Diabetes Melitus AND NON," *Edu Sci. J.*, vol. 1, no. 1, pp. 25–36, 2020.

[3] P. Susilawati, Ahmad, Moelyono, "Farmaka Farmaka," *Farmaka*, vol. 14, no. 2, pp. 82–96, 2014.

[4] and S. Hutahaean, Banjarnahor, Darsini, Ilyas, "The effect of Saurauia vulcani Korth . leaves extract on penile corpus cavernosa microstructure and the quality of sperm in alloxan-induced diabetic mice The effect of Saurauia vulcani Korth . leaves extract on penile corpus cavernosa microstructure and t," vol. 1116, no. 0520, pp. 6–12, 2018.

[5] M. A. Antika, S. Ilyas, and M. I. Sari, "Effect of *Lawsonia inermis* Linn . Ethanol Extract on the Superoxyde Dismutase Activity in Hyperglycemic Rattus norvegicus," pp. 79–85, 2016.
[6] G. A. Siregar, D. K. Sari, T. Sungkar, M. S. Bachri, S. Yuliani, and A. K. Sari, "Effect of *Lawsonia innermis* (Linn) leaves ethanolic extract on blood glucose and malondialdehyde level in alloxan-induced diabetic rats Effect of *Lawsonia innermis* (Linn) leaves ethanolic extract on blood glucose and malondialdehyde level in alloxan-i," *IOP Conf. Ser. Earth Environ. Sci.*, vol. 130, no. 1, pp. 1315–1755, 2018.
[7] C. M. Zega, Wowor, "Uji beberapa dosis ekstrak buah mengkudu (*Morinda citrifolia*L .) terhadap kadar glukosa darah pada tikus wistar (Rattus norvegicus) yang diinduksi aloksan," *J. e-Biomedik*, vol. 4, no. 2, 2016.
[8] C. L. T. Chang, Y. Lin, A. P. Bartolome, Y. Chen, S. Chiu, and W. Yang, "Herbal Therapies for Type 2 Diabetes Mellitus : Chemistry , Biology , and Potential Application of Selected Plants and Compounds," vol. 2013, 2013.
[9] A. Patil, S. Nirmal, S. Pattan, V. Tambe, and M. Tare, "Antidiabetic effect of polyherbal combinations in STZ induced diabetes involve inhibition of α -amylase and α -glucosidase with amelioration of lipid profile," vol. 2, no. 1, pp. 46–57, 2012.
[10] R. S. Khairani, Yuniarti, "DOI : 10.24036/eksakta/vol19-iss01/123," vol. 19, no. 1, 2018.
[11] M. I. Sari, S. Ilyas, T. Widyawati, and M. A. Antika, "Effect of *Lawsonia innermis* (Linn) leaves ethanolic extract on blood glucose and malondialdehyde level in alloxan-induced diabetic rats," *IOP Conf. Ser. Earth Environ. Sci.*, vol. 130, no. 1, 2018.
[12] S. Nagalingam, C. S. Sasikumar, and K. M. Cherian, "Academic Sciences," vol. 5, pp. 4–6, 2012.
[13] N. Agrawal, M. K. Agrawal, T. Kumari, and S. Kumar, "Correlation between Body Mass Index and Blood Glucose Levels in Jharkhand Population," vol. 4, no. 8, pp. 1633–1636, 2017.
[14] J. Wang, R. Yan, J. Wen, X. Kong, H. Li, and P. Zhou, "Association of lower body mass index with increased glycemic variability in patients with newly diagnosed type 2 diabetes : a cross-sectional study in China," vol. 8, no. 42, pp. 73133–73143, 2017.
[15] D. L. Hickman and M. Swan, "Use of a Body Condition Score Technique to Assess Health Status in a Rat Model of Polycystic Kidney Disease," vol. 49, no. 2, pp. 155–159, 2010.
[16] F. R. Zakaria and E. Prangdimurti, "The Effect Of Roselle Extract (*Hibiscus sabdariffa* Linn.) On Blood Glucose Level And Total Antioxidant Level On Diabetic Rat Induced By Streptozotocin The Effect of Roselle Extract (*Hibiscus sabdariffa* Linn.) On Blood Glucose Level And Total Antioxid," no. February 2017, pp. 7–16, 2014.
[17] A. Rohilla and S. Ali, "Alloxan Induced Diabetes : Mechanisms and Effects," vol. 3, no. 2, pp. 819–823, 1943.
[18] A. Ben, M. Trigui, G. Culioli, Y. Blache, and S. Jaoua, "Antioxidant constituents from *Lawsonia inermis* leaves : Isolation , structure elucidation and antioxidative capacity," *Food Chem.*, vol. 125, no. 1, pp. 193–200, 2011.
[19] C. Dunnill *et al.*, "Reactive oxygen species (ROS) and wound healing: the functional role of ROS and emerging ROS-modulating technologies for augmentation of the healing process," *Int. Wound J.*, vol. 14, no. 1, pp. 89–96, 2017.
[20] M. M. Dan, P. Sarmah, D. Rao Vana, and Dattatreya A, "Wound Healing: Concepts and Updates in Herbal Medicine," *Int. J. Med. Res. Heal. Sci.*, vol. 7, no. 1, pp. 170–181, 2018.
[21] P. C. Situmorang, S. Ilyas, and S. Hutahaean, " Effect of Combination of Nano Herbal Andaliman (*Zanthoxylum acanthopodium* DC.) and Extra Virgin Olive Oil (EVOO) to Kidney Histology of Preeclampsia Rats ," *IOP Conf. Ser. Earth Environ. Sci.*, vol. 305, p. 012081, 2019.
[22] P. C. Situmorang and S. Ilyas, "Study of preeclampsia in placenta, kidney, and hepatic diseases," *Asian J. Pharm. Clin. Res.*, vol. 11, no. 11, pp. 21–28, 2018.
[23] P. C. Situmorang and S. Ilyas, "Review: Germinal cell apoptosis by herbal medicine," *Asian J. Pharm. Clin. Res.*, vol. 11, no. 9, pp. 24–31, 2018.
[24] P. C. Situmorang and S. Ilyas, "Description of kidney histology of mus musculus after giving nano herbal *Rhodomyrtus tomentosa* (Haramonting)," *Int. J. Ecophysiol.*, vol. 01, no. 01, pp. 26–33, 2019.
[25] Masfria, U. H. Hap, M. P. Nasution, and S. Ilyas, "Cytotoxic activity, proliferation inhibition and apoptosis induction of *Rhaphidophora pinnata* (L.F.) schott chloroform fraction to MCF-7 cell line," *Int. J. PharmTech Res.*, vol. 6, no. 4, pp. 1327–1333, 2014.

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