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ANTIDIABETIC ACTIVITY OF ETHANOL EXTRACT OF SONI LEAVES (*DILLENIA CELEBICA* HOOGLAND.) ON BLOOD GLUCOSE LEVELS AND PANCREATIC HISTOLOGY OF MALE WISTAR RATS GLUCOSE-INDUCED

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Abstract:

Objective: *Determine the potential, effectiveness and histology of pancreatic organs of wistar male rats with type II diabetes after glucose induction by giving ethanol extract of soni leaves (Dillenia celebica Hoogland.).*

Method: *Experimental with pre-post test randomized control group design. One-Way Anova Statistics to see a decrease and percent decrease in blood glucose levels. The histology of the pancreatic organs is based the number of endocrine cells the islet of Langerhans using a microscope. Diabetes mellitus modeling by oral glucose-induced dose 20g/kgbw. The rats were divided into 6 groups, namely Normal Control, Negative Control, Positive Control and Group given ethanol extract of Soni leaves at a dose 29,78 mg/kgbw, 59,57 mg/kgbw, 120,74 mg/kgbw, respectively.*

Results: *Ethanol extract of soni leaves has the potential as antidiabetic which was significantly different ($p<0.05$) to the negative control group and at a dose 120.74 mg/kgbw has the same effectiveness as glibenclamide ($p<0,05$) in reducing blood glucose levels. And the histology of the pancreatic organs compared to the positive control group on a dose 120,74 mg/kgbw has the same ability to regenerate endocrine cells as indicated by improvements the Langerhans islet based the number of regenerated endocrine cells with the number of cells 415 and 410 cells.*

Conclusion: *Ethanol extract of soni leaves has the potential and effectiveness in reducing blood glucose levels and has the effectiveness of regenerating pancreatic β cells on langerhans.*

Keywords : Dillenia celebica Hoogland, Glucoce, Antidiabetic, Pancreatic Histology.

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INTRODUCTION:

The incidence of DM every year continues to increase, both in the world and in Indonesia. International Diabetes Federation (IDF) states that in 2017 there are 424.9 million people in the world who carry DM and predicted that by 2045 it will increase to 628.6 million. Indonesia ranks 7th after China, India, the United States, Brazil, Russia and Mexico as the most cases of DM in the world with a number of cases of 10 million[1]. Based on the annual report of the Southeast Sulawesi cases of diabetes mellitus has increased from number 9 in 2015 to number 5 in 2016 out of the 10 biggest diseases in Southeast Sulawesi where the proportion of the incidence of type II DM is higher than type I DM[2,3]. Therefore, diabetes mellitus now receives a lot of attention from various parties in prevention and management efforts. Diabetes mellitus (DM) is a metabolic disorder characterized by an increase in blood glucose levels (hyperglycemia). This is related to the abnormal state of carbohydrate, fat and protein metabolism due to impaired insulin secretion, decreased insulin sensitivity or both and if long lasting results in complications[4].

Management and prevention of complications in patients with DM is done through regulating blood glucose levels well with nonpharmacological and pharmacological therapies. Treatment of diabetes is usually done by administering injections of insulin, oral antidiabetic drugs that usually use synthetic drugs that number two or more drugs. Treatment of DM is a long-term treatment. Long-term use of many drugs can cause patient non-compliance to increase. In addition, there is also an increase in drug interactions and side effects, as well as increased costs to be incurred by patients[5]. This encourages researchers to find alternative drugs with better efficacy and allows diabetics to have many treatment options, thereby increasing the chances of recovery, at least with controlled blood glucose levels and minimal side effects and relatively more economical costs such as utilizing traditional medicine originating from plants[6].

Traditional medicine mostly uses potion that come from plants from roots, stems, seeds, flowers, leaves or bark. Parts of the plant contain secondary metabolites consisting of alkaloids, steroids, flavonoids, tannins, triterpenes and saponins. These secondary metabolites have biological activity. One of them is antidiabetic[7].

Research on the discovery of new antidiabetic agents from plants is still ongoing, although it is well known that more than 400 plants have hypoglycemic activity. One of the medicinal plants that has not been widely studied scientifically is soni plants. Parts of plants that are thought to have antidiabetic properties are the leaves. Soni leaves are endemic to southeast sulawesi. Soni is a family of dilleniaceae. Soni is usually used by surrounding communities such as bark used to treat vomiting of blood [8]. The compounds contained in soni leaves are flavonoids, tannins, saponins and triterpenes[9]. It is known that the content of these compounds may act as antidiabetic[10]. Unfortunately for research on the effect of soni leaves as antidiabetic in test animals has never been done. Based on the description of the background above, the researchers felt interested in conducting a study on the antidiabetic activity of ethanol extract of soni leaves (Dillenia celebica Hoogland) in glucose induced male wistar rats and histopathology of the pancreatic organs of male rats wistar strains that have diabetes mellitus Type II by administering ethanol extract of soni leaves (*Dillenia celebica* Hoogland).

METHODS:

Type of research:

This research is an experimental research model pre-post test control group design by measuring the effect of ethanol extract of soni leaves (DilleniacelebicaHoogland) on blood glucose levels in male wistar rats (Rattusnovergicus) and analysis of data using descriptive methods that are presented in the form of images.

The study was conducted from January to September 2018 at the Pharmacy Laboratory of the Faculty of Pharmacy, Laboratory of Medical Faculty at Halu Oleo UniversityKendari and Private Clinic Makassar. The implementation of this research has been approved by the Ethical Committee of the University ofHalu Oleo Medical School through the publication of Ethical Clearance (EC).

Materials:

The ingredients used in this study were soni leaves (DilleniacelebicaHoogland), male wistar strain (Rattusnovergicus), distilled water, 70% alcohol, 80%, 96%, anhydrous acetic acid, concentrated sulfuric acid, formalin neutral buffer 10 %, emil alcohol, 96% ethanol, ether, 1% FeCl3, sucrose, glibenclamide, glucose, concentrated HCl, 2N HCl, foods high in carbohydrate and fat (MTKL), Sodium Carboxymethyle Cellulose (Na CMC), NaOH 2M, reagent Dragendrof, powder Mg, xylol, paraffin, Haematoxylin and Eosin.

The tools used are 1 set of reflux tool, stirring rod, blender (Philips), vial bottle, porcelain cup, funnel,

beaker (Pyrex), measuring cup (Pyrex), glucometer (Autocheck), hot plate, cannula, rotary evaporator (Buchi), glucometer strip, spoit, analytical scales (Precisa), rat scales, waterbath, tools for making pancreatic histology preparations, namely: Cutting board, scalpel knife, tweezers, tissue cassette, automatic processor machine (Kedee®), vacuum machine, blocking machine, freezer (LG), microtome machine (Kedee®), microtome knife, water bath (Kedee®), object glass, cover glass, special rack for coloring, microscopes.

Variable of Research:
The variables in this study consist of 2 variables, namely the independent variable and the dependent variable. The independent variable in this study was the variation in the dosage of ethanol extract of soni leaves. While the dependent variable in this study was a decrease in blood glucose levels and a decrease in blood glucose levels and a description of the hispatology of animal pancreatic organs to try diabetes mellitus by looking at descriptive data on endocrine cell repair on the islet of langerhans and the number of regenerated endocrine cells.

Procedur:
Preparation Sample:
Soni leaves samples (DilleniacelebicaHoogland) were obtained from desaWarangga, KecamatanKatobu, KabupatenMuna, Sulawesi Tenggara. Soni leaves samples obtained as much as 4 kg were washed to remove soil and other impurities attached to soni leaves. Washing is done in running water. After washing, the sample is drained so that excess washing water flows. Scaffolding is done using a knife to facilitate the drying process. Soni leaf samples that have been chopped are dried. Drying is done by aerating and coated with black cloth to avoid direct sunlight because ultraviolet light from the sun can cause damage to the chemical content of the dried material and also has good air circulation so that it optimizes the drying process Dry sorting is then carried out to separate the objects foreign objects such as unwanted plant parts that are still present and left behind in dry simplicia. Soni leaf samples are then mashed. The goal is to enlarge the surface area of soni leaves, so that the contact between the material and the solution of the dancer is greater and the spread takes place faster and the active compounds are more abundant.

Extraction:
The extraction method used is the reflux method. 500 gram of soni leaves simpisia is put into 100 g round bottom flask, then soaked with 300 ml ethanol 96% solvent then heated. Filtrat was then evaporated to obtain an ethanol extract of soni leaves.

Preparation of materials:
Determination of Glucose Dosage and Making High Fat Foods:
Based on research to make the condition of hyperglycemia in rats given glucose 20 g/kgBB[12]. Glucose is given to oral rats. Making 5 kg of high fat food consists of 1 kg beef fat, standard 4 kg food, 4 grain duck egg yolk[13].

Preparation of Dosage glibenclamid:
The therapeutic dose of glibenclamide in humans is 5 mg. The results of conversion from humans with a body weight of 60 kg to rats weighing 200 g are equal to 0.45 mg / kg body weight. Glibenclamidesuspension are made by dissolving glibenclamide in Na CMC 1%.

Preparation of Na CMC 1% Suspension:
Na CMC suspension is made 1 g of Na CMC into a chemical glass and then adding 10 ml of aquadestto stir. After that it is added with aquadestuntil the total volume of 100 ml solution is stirred while heated on a hot plate. Cool for 15 minutes until a transparent mass is obtained, then stir until homogeneous.

Antidiabetic Activity:
Acclimatization of Test Animals:
The study used male wistar rats (Rattus norvegicus) aged 2-3 months with a weighing 200-300 grams. Animal use of male wistar rats for several reasons, among others, is easy to breed, easy to maintain, easy to draw enough blood through the tail to get capillary blood, its physiology is thought to be identical to humans[14]. Acclimatization of animals is carried out for 7 days to familiarize rat test animals living in the environment and given enough food and drink. Each group is given the same food. At the end of the acclimatization fasting blood glucose levels were examined in experimental animals[15].

Treatment of Test Animals:
Test animals are acclimatized for 7 days by providing standard animal feed. Then each ratswas taken for blood which had been fasted for 8-12 hours and measured the initial blood glucose level. Furthermore, all groups except the normal group were induced orally with 20g/kgBB of glucose 3 times a day and were given additional foods high in carbohydrates and fats twice a day for 21 days to increase blood glucose levels of the test animals. After 21 days after administration of glucose the blood glucose level of the rats was measured again, if there was an increase in blood glucose levels in rats >135 mg/dL then the

rats were considered to have diabetes. Then therapy is carried out on test animals. Each group was treated: Normal control, 1% NaCMC, negative control, 1% NaCMC, positive control, glibenclamide 0.45 mg / kgBB, KDS I soni ethanol extract dose 29.78 mg / kgBB, KDS group II soni ethanol extract dose 59.57 mg / kgBB and KDS III group Soni ethanol extract dosage 120.74 mg / kgBB. Therapy was carried out for 14 days and then measured glucose levels in test animals.

Blood glucose level measurement of test animals:
Measurement of blood glucose levels using glucometers. Before taking blood, the glucometer is first activated, then put the test strip into the glucometer. Blood is taken from the tip of the tail using a blood lancet, then drops on the test strip on the glucometer and automatically the blood glucose level will be measured and the results can be read monitored glucometer.

Analysis Histopathological:
Harvesting of the Pancreatic Organ:
All mice are generalized to ether. Then the mice were dissected and the rat's pancreatic organs were taken. The pancreatic organ is then washed with physiological NaCl 0.9% and fixed with 10% buffer neutral formalin (BNF) followed by making histopathological preparations.

Making Histopathological Preparations:
Fixation:
Tissue fixation by immersing in 10% phosphate buffer formalin for 24 hours, then slicing (trimming) with ± 3 mm thickness so that it can be put in a box to be processed in a tissue processor.

Dehydration:
The tissue inside the processor cassette is inserted into a tissue processor using multilevel alcohols consisting of alcohol 70%, 80%, 96%. Then cleared into xylolI and xylol II.

Embedding and Printing (Blocking):
Then the tissue is put into liquid paraffin at 56 ° C for 2 hours 2 times. The tissue is then taken with tweezers, followed by blocking using a paraffin block.

Cutting:
Cutting (cutting) is done using a microtome of 3-5 µm thickness. The tissue was developed in a water bath and then captured using glass preparations for further coloring using HE staining.

Staining of Hematoxylin Eosin (HE):
Staining was carried out by means of a glass top of the object soaked in xylol, then the preparations were soaked in alcohol 70%, 80% and 96%, then washed with distilled water, then into hematoxylin 7 minutes, washed back into distilled water, then deep eosin 5 minutes, in soak it back into alcohol with a level of 96%, 80% and 70%, purified again into xylol. Preparations are dried and mounted using an entanglement.

Observation of Histopathology:
Histopathological preparations were examined under each microscope at 5 microscopic view fields. Examination with a microscope is carried out with 400x magnification. Histopathological changes observed included the presence of degeneration and necrosis.

Data processing:
The data obtained is made in the form of tables and diagrams, then the results are described.

Statistical Analysis:
Analysis of the data used in this study uses the One-way Analysis of Variance (ANOVA) method with the data requirements of each group normally distributed. This data analysis method used Statistical Package For Social Science (SPSS) software, with a confidence level of 0.05 or 95%. As a follow-up test used post hoc Least Significance Difference (LSD) analysis and data analysis using descriptive methods are presented in the form of images.

RESULTS:

Profile of Blood Glucose Level Before and After Modeling:
The following is a modeling diagram of initial blood glucose levels and blood glucose levels after modeling:

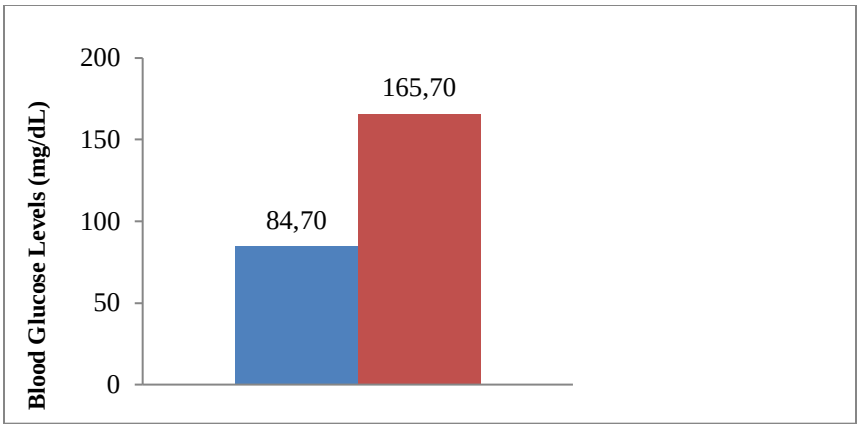

Figure 1. blood glucose level before and after modeling

Rat Blood Glucose Level Measurement Data:

The following is a table of data on the average results of measuring blood glucose levels in rats during therapy :

Table1. Average blood glucose level during theraphy

Kelompok Perlakuan	Kadar Glukosa darah (mg/dl) ± SD		
	Hari ke-0	**Hari ke-7**	**Hari ke-14**
KN	93,75 ± 6,94	92,50 ± 5,25	94,50 ± 3,10
K(-)	161,00 ± 7,07	157,00 ± 5,47	153,75 ± 6,07
K(+)	196,25 ± 5,43	126,50 ± 12,87	97,00 ± 2,44*
KD I	172,00 ± 5,88	153,00 ± 8,28	137,50 ± 3,10*
KD II	181,75 ± 4,71	142,50 ± 4,04	121,25 ± 6,84*
KD III	190,50 ± 7,18	137,00 ± 3,91	102,00 ± 6,6*

Information:

H7 = Blood glucose level therapy 1 week

H14 = Blood glucose level therapy 2 week

(*) There were significant differences ($p < 0.05$) for the negative control group

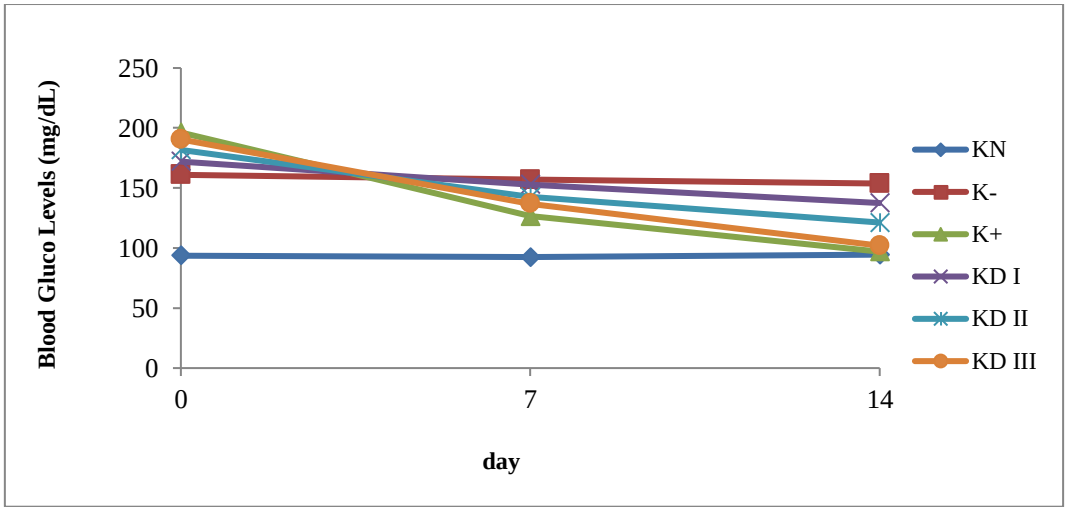

Figure2. Average profile glucose level during therapy

Percent Decrease in Rats Blood Glucose Levels During Therapy

Table 2. Percent decrease in rats blood glucose levels during therapy

Kelompok Perlakuan	Rata-rata persen penurunan ± SD (%)	
	Day-7	Day-14
KN	1,07 ± 6,54	-1,05 ± 4,95
K(-)	2,44 ± 1,55	4,00 ± 2,73
K(+)	35,61 ± 5,32	50,56 ± 0,73*
KD I	11,07 ± 2,59	20,02 ± 1,81*
KD II	21,52 ± 4,07	33,19 ± 5,23*
KD III	31,20 ± 1,56	46,00 ± 2,29*

(*)There were significant differences ($p < 0.05$) for the negative control group

Information :

KN : normal rats given Na CMC 1%
K(-) : diabetic rats given Na CMC 1% as negative control
K(+) : diabetic rats given glibenklamid 0,45 mg/kgBB
KD I : diabetic rats given soni extract at a dose 29,78 mg/kgBB
KD II : diabetic rats given soni extract at a dose 59,57mg/kgBB
KD III : diabetic rats given soni extract at a dose 120,74mg/kgBB

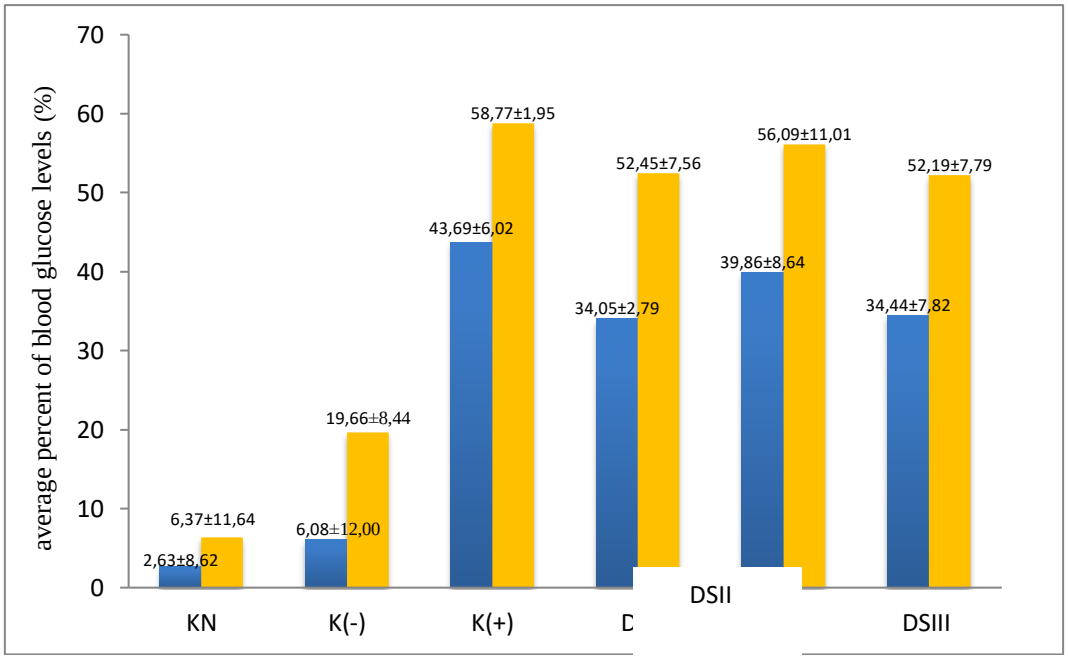

Figure3. Percent decrease average in rats blood glucose levels during therapy

Number of Endocrine Cells on Langerhans Islet

Table 5. Endocrine Cell Number in Langerhans Islet

No	Trial Group	Number of Endocrine Cells
1.	Normal group	450Cell
2.	Negative Control Groups (K(-))	220 Cell
3.	Positive Control Groups(K(+))	415 Cell
4.	KD I (at a dose 29,78 mg/kgbw)	295 Cell
5.	KD II (at a dose 59,57 mg/kgbw)	360 Cell
6.	KD III (at a dose 120,74 mg/kgbw)	410 Cell

DISCUSSION:

Test Animal Modeling:

Experimental animal modeling was carried out using the oral glucose induction method. The glucose dose used for inducing rats was 30 each, which was 20 g / kgBB 3 times a day for 21 days and in addition additional food was given Foods High in Carbohydrates and Fats (FHCF). FHCF is given as an additional food to model animal type 2 diabetes mellitus and with this administration it can increase triglyceride levels in the body and can cause several medical conditions such as diabetes mellitus[16]. The success of animal modeling is seen from the results of rat blood sugar levels. Blood collection is carried out every week to measure fasting blood glucose levels (GDP). Modeling of diabetic rats on the 21st day was successfully performed seen from blood sugar levels >135mg / dL in Figure 1.

The results showed that an increase in fasting blood glucose levels in mice after being given glucose 20 g/kgbb for 21, wherein the initial blood glucose level was 84.70 mg/dL and after induction to 165.70 mg/dL. Increased glucose levels in ratsthat exceed levels >135 mg/dL[17] categorized as diabetic rats. The increase in Fasting Blood Glucose levels was then proven by statistical testing using the t-Test method. The test results showed the success seen in the results of the analysis using the t-Test showed a sig value: ($p<0.05$) so it can be said that there is a difference between blood glucose levels before modeling and blood glucose levels after modeling. Giving glucose solution causes an increase in high blood glucose levels in test animals. This shows that excessive glucose consumption causes β cells to not work optimally to produce the hormone insulin in response to high blood glucose levels[18].

Antidiabetic Activity Tes:

The antidiabetic activity of soni leaves ethanol extract (*Dillenia celebica* Hoogland) was assessed based on its potential in reducing blood glucose levels and its effectiveness on positive control of glibenclamide in diabetic rats (> 135 mg / dL). Therapy is carried out once daily orally for 14 days for each treatment group. Then the observations were carried out at the 1st and 2nd week of therapy by taking blood from rat test animals in order to see a decrease in blood glucose levels after administration of extracts.

The results of the study show in Table 3, there was a decrease in blood glucose levels in the treatment group when the therapy was given for 14 days. But the 14th day KD I group showed 137.50 mg / dL of rat blood glucose levels, blood glucose level in the group was still in the diabetes range (<135 mg / dL), this meant that the KD I group had no potential to be antidiabetic at the time giving extract for 14 days. Whereas KD II group rat blood glucose levels 121.50 mg / dL and KD III rat blood glucose levels of 102.00 mg / dL showed that both doses could reduce rat blood glucose levels (<135 mg / dL) this means that for 14 the day of administration of KD II and KD III extracts can improve the condition of diabetic rats and show that the KD II and KD III groups have the potential to reduce blood glucose levels in diabetic rats.This is in line with the post hoc LSD test by looking at rat glucose levels in the DS II and DS III test groups against the negative control group (K-) indicating that on the 7th and 14th day the blood glucose level of the KD III group was 102.00± 6.16 shows a significant difference ($p<0.05$) for the negative control group 153.75±6.07 and KD II 121.25 ± 6.84 showing significant differences ($p <0.05$) for the negative control group 153, 75 ± 6.07 which means that the ethanol extract of the leaves of Soni KD II and KD III has been able to reduce glucose levels significantly. This shows that Groups KD II and KD III have the potential to reduce blood glucose levels in rats.

In this study there was also a decrease in blood glucose levels in the negative control group (K-) but still in the range of diabetes this indicates that the pancreas can still secrete insulin, although glucose induction can inhibit insulin secretion in the pancreas, but glucose induction does not damage β cells the pancreas in total, so that it can still produce insulin but the insulin produced is insufficient to convert glucose into a source of energy for the body so that glucose will remain in the blood and blood glucose levels but high. Giving extracts in the first week of therapy has caused a decrease in blood glucose levels in diabetic mice but still shows a significant difference ($p<0.05$) for the normal group. Whereas in the second week of therapy the KD II and KD III test groups showed the same blood glucose level as normal (GDP <135 mg / dL).

The effectiveness of extracts was assessed by comparing the average reduction in blood glucose levels of the three dose groups (KD I, KD II and KD III) with the positive control group (K(+)). The results of the average decrease in blood glucose levels on the 7th and 14th days showed that all doses had decreased blood glucose but at the first dose they were still in the range of diabetic rats. Based on Table 3, on the 7th day rat blood glucose levels in the dosage group KD III 137.00±3.91 showed no significant difference for the positive control group (K(+)) 126.5±12.87 which

means that at the third dose of soni leaf ethanol extract possesses the effectiveness of reducing blood glucose levels which are almost the same as the positive control group (Glibenklamid). On the 14th day blood glucose levels of KD III group 102.0±6.16 still showed no significant difference to the positive control group (K(+)) 97.00±2.44 while the KD I group 137.50 ± 3.10 shows that there is a significant difference ($p<0.05$) for the positive control group (K(+)) 97.00±2.44 as well as KD II which means the effectiveness of reducing blood glucose levels in the positive control group is better compared to KD I and KD II groups. This shows that the ethanol extract of KD III soni (Dillenia celebica Hoogland) leaves (120.74 mg/kgbw) has almost the same effectiveness in reducing blood glucose levels in the positive control group given glibenclamide.

The average profile of a decrease in fasting blood glucose levels in mice after therapy showed an average percentage decrease of the three dose groups (KD I, KD II, and KD III) that had a higher percent decrease compared to the negative control group (K(-)) thus showing that the ethanol extract of soni leaves (Dillenia celebica Hoogland) can reduce blood glucose levels in rats. However, from the three test dose groups, the DS III group (dosage 120.74 mg/kgBB) had a higher percentage reduction in blood glucose levels than KD I (at a dose 29.78 mg / kgbw) and KDS (at a dose 59.57 mg/kgbw)) and the results of the post hoc test showed no significant difference in the reduction in blood glucose levels between KD III and the positive group. In addition, a decrease in blood glucose levels in the KD III group (at a dose of 120.74 mg/kgbw) to the normal group showed no significant difference, which meant a decrease in KD III blood glucose levels reached normal blood glucose levels.

A dose that has a near-normal effect shows that the active compounds contained therein are optimum effective concentration, whereas in other doses it is still lacking so that it has a less effective and inadequate effect, resulting in smaller antihyperglycemic effects [19].The higher the extract dose given, the greater the effect. This is due to the high dosage given so that the concentration of the active compound in the extract is also getting higher and causes the ability to suppress or anti-force to bestronger[20].

The decrease in blood glucose levels of rats in the group given soni ethanol extract (*Dillenia celebica* Hoogland) was thought to be caused by the presence of flavonoids and tannins contained in soni ethanol extract to help repair damaged pancreatic beta cells so as to increase insulin secretion. Flavonoids can reduce blood glucose levels with their abilities as antioxidants. Flavonoids are protective against β cell damage as a producer of insulin and can increase insulin sensitivity[21]. Tanin has a decrease in blood glucose activity by inhibiting the work of α glucosidase and shrinking the small intestinal epithelial membrane thereby reducing absorption of food essence and as a result inhibits glucose intake and the rate of increase in blood glucose is not too high[22]. Saponin works by changing the intestinal membrane to become more permeable so that the absorption of glucose becomes inhibited, saponin is also able to regenerate the pancreas which causes an increase in the of pancreatic β cells and Langerhans so that insulin secretion has increased [23].

Observation of Pancreatic Organ Histology:

Observation of the histopathology of diabetes mellitus using experimental pancreatic organs which have been surgically processed by microscopic observation using Hematoxilin-Eosin staining by looking at endocrine cell repair on the langerhans islet. Endocrine cells that are scattered throughout the pancreatic organs are shaped like islets and are traversed by blood capillaries in which there are 3 cells, alpha cells, beta cells, and delta cells. This beta cell serves to secrete insulin.

Histological testing was done by calculating the number of pancreatic β cells to see morphological changes due to diabetes[24]. The histopathological description of the pancreas was observed using a microscope (Olympus) using a 400x magnification. Endocrine cell count was obtained by manually counting endocrine cells on the islet of Langerhans using 5 visual fields.

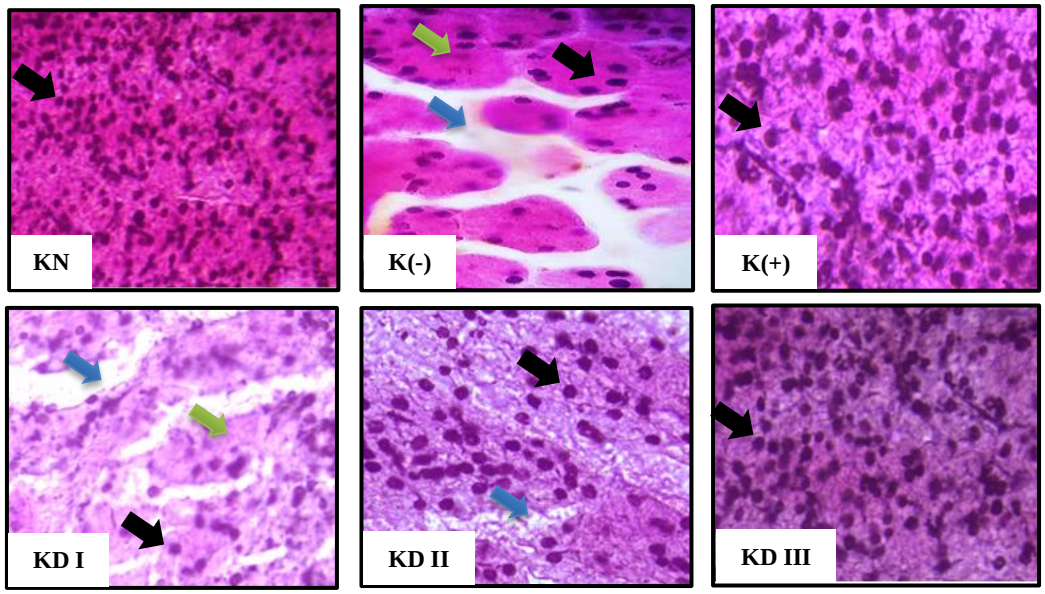

Figure 4. Langerhans Islet Cell Histopathology uses HE Staining, with a Magnification of 400x.

Description: KN (Normal Group), K (-) (Negative Group), K (+) (Positive Group), KD I (Soni Leaf Dosage I), KD (Soni Leaf Dosage II) and KD III (Soni Leaf Dosage III). = normal cell, = necrosis, = degeneration.

DESCRIPTION:

KN (Normal Group), K (-) (Negative Group), K (+) (Positive Group), KD I (Soni Leaf Dosage I), KD (Soni Leaf Dosage II) and KD III (Soni Leaf Dosage III). = normal cell, = necrosis, = degeneration. Based on Figure 4, the histological picture of langerhans islet cells in normal groups of mice on the 14th day of therapy, the appearance of langerhans islet groups of normal mice can be seen in the presence of regularity of endocrine cell lines that spread on the islet of langerhans. The purple endocrine cell nucleus is of the same large and uniform shape and the endocrine cells are tight, intact, not experiencing necrosis and cell degeneration.Negative group (K(-)) on therapy on day 14, there was damage to the langerhans islet which experienced necrosis or cell death characterized by the formation of empty spaces on the islet of langerhans, degenerative which was characterized by the beginning of the disappearance of the cell nucleus on the islet langerhans, non-uniform cell nucleus. This is because the test animals are given excessive glucose but are not given therapy and only 1% Na CMC is given so that insulin resistance is characterized by a decrease in endocrine cells and morphologically damage occurs in the form of necrosis and degeneration on the islet langerhans.Positive group (K(+)) in the 14th day therapy, in figure 7 there is improvement towards normal cells characterized by a uniform arrangement of endocrine cells and no degeneration and necrosis with dense and dense cell nuclei. This is due to the administration of glibenclamide in test animals, where glibenclamide is an oral antidiabetic drug in the sulfonylurea group whose mecenism stimulates pancreatic β cells to stimulate insulin secretion. KD I group 29.78 mg/ kgbw on the 14th day can be seen on the islet of Langerhans there are endocrine cells that experience necrosis which is characterized by the presence of empty space on the islet langerhans due to cell death, degenerative characterized by the beginning of loss of cell nucleus on the langerhans and non-uniform cell nucleus. The KD II group 59.57

mg/kgbw in the 14th day therapy can be seen showing an improvement in endocrine cells on the islet of Langerhans with a uniform arrangement of endocrine cells and cell regeneration in the islets of Langerhans which is indicated by reduced empty space due to necrosis or death cell. And for the KD III 120.74 mg/kgbw group in the 14th day therapy it can be seen showing an improvement in endocrine cells on the islet of Langerhans which has improved towards normal with a tight array of endocrine cells with a uniform cell nucleus, and not there is an area that experiences necrosis and degeneration in cells on the islet of langerhans.

Histological images of the langerhans islet in the KD I group have the ability to regenerate endocrine cells on langerhans. The KD II and KD III groups have the ability to regenerate endocrine cells on the islet of Langerhans characterized by a reduced area of necrosis in KD II and KD III where there is no area of necrosis and cell degeneration on the islet of langerhans Compared with the positive control group (K(+)), KD III has the ability to regenerate endocrine cells which is indicated by better improvement on the islet of Langerhans based on the number of regenerated endocrine cells undergoing regeneration of 415 and 410 cells. The concentration of soni leaf extract is the most effective in reducing levels of gulah animal blood test and repair pancreatic β cell damage, namely KD III.

Cell repair on the langerhans islet was thought to be due to the content of secondary metabolites in the form of flavonoids, tannins and terpenoids which could act as antioxidants that could repair cell cells of Langerhans. The mechanism of antioxidants in repairing pancreatic β cell damage is antioxidants stabilizing free radicals by complementing the lack of electrons which have free radicals and inhibiting the occurrence of chain reactions from the formation of free radicals which can cause destructive oxidative stress [24].

CONCLUSION:

Ethanol extract of soni leaves (*Dillenia celebica* Hoogland.) has the potential and effectiveness in reducing blood glucose levels and has the effectiveness of regenerating pancreatic β cells on langerhans.

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