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The Effect of Aloe Vera Extract on Blood Glucose Levels in Streptozotocin-Induced Rats

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Abstract

Aloevera can protect and restore the function of damaged pancreatic beta cells. The content of aloe vera can work like insulin, and lower blood glucose even though all beta cells have degenerated. The aim of the study was to find out the effect of aloe vera extract on the regulation of blood glucose levels in rats induced by streptozotocin. The study was true experimental randomized pre-post test control group design. The sampling technique used simple random sampling consisting of 20 wistar strain rats divided into 4 groups, namely the placebo control group, treatment group with a dose of 250 mg/dl, a dose of 350 mg/dl, and a dose of 1000 mg/dl. Rats were given STZ injection on day 8 after acclimatization. The independent variable was aloe vera extract. The dependent variable was blood glucose levels. The intervention of giving aloe vera extract was given for 9 days. Data were analyzed by Paired t Test and ANOVA. The results showed that there was an effect of aloe vera extract at a dose of 350 mg/kgBW on blood glucose levels with a paired t test of 0.022. The ANOVA results showed that aloe vera extract at a dose of 350 mg/kgBW had the highest effectiveness with a p value of 0.05. The chromium, alprogen, and flavonoid in aloe vera will improve the beta function of the pancreas in producing the hormone insulin. Damage to the islets of Langerhans cells in the pancreas will be inhibited and restore the sensitivity of the insulin receptor cells.methods that are attractive to high school students and carried out consistently.

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INTRODUCTION

Diabetes Mellitus (DM) is also known as the great imitator because it causes damage to the body's organs as a whole, both anatomically and functionally (Aini et al., 2011). DM is a metabolic disorder disease that is chronic and complex with the characteristics of hyperglycemia arising from absolute or relative insulin deficiency (Aveonita, 2015; Pradono, 2011; Sugandha & Lestari, 2015). Type 2 diabetes hyperglycemia is caused by cellular insensitivity to insulin. In addition, insulin secretion defects occur, namely the inability of the pancreas to produce sufficient insulin to maintain normal plasma glucose (Arif et al., 2020; Corwin, 2009). Many complications can occur due to hyperglycemia such as hypertension, neuropathy, coronary heart disease, nephropathy, and gangrene (Aveonita, 2015).

In hyperglycemic conditions, glucose will undergo a non-enzymatic glycosylation reaction spontaneously with hemoglobin to form glycated hemoglobin. Glucose can be oxidized before binding to hemoglobin as well as glucose after binding to hemoglobin will be oxidized and produce Reactive Oxygen Species (ROS). ROS will increase the expression of Tumor necrosis factor (TNFα) which causes insulin resistance through decreased autophosphorylation of insulin receptors, changes in insulin receptor substrate (IR-s) to inhibitors of receptor tyrosine kinase activity, decreased insulin-sensitive glucose transporter (GLUT-4), alter the function of cells, and increase the circulation of fatty acids. The antioxidant activity of aloe vera extract increases glucose tolerance by preventing blood glucose oxidation, reducing the potential of enzymes that play a role in the transfer of phosphate groups on glucose which is the initial stage of the glycosylation process and improving oxidative stress (Pertiwi & Rahayuningsih, 2012).

Successful treatment of DM patients takes a long time because DM is a chronic disease that will last a lifetime and is very complex (Aini et al., 2011; Arif, 2018). Monitoring the status of blood glucose levels on a regular basis in DM patients is the core of treatment (Kotwal & Pandit, 2012). The success of DM treatment can also be done in several ways, such as controlling blood glucose levels, physical activity, diet, weight loss, blood pressure/lipid management, and others. All of these activities are also to prevent micro-vascular and macro-vascular diseases (Sucharita et al., 2018; Wasir et al., 2018). Adequate control of glucose levels will reduce the risk of complications caused by diabetes mellitus (Kotwal & Pandit, 2012).

WHO predicts an increase in the number of patients in 2000 from 8.4 million to around 21.3 million in 2030 (Sugandha & Lestari, 2015). Hospital Annual Report 2012 (as of May 31, 2013), the most cases of disease were outpatients at type B hospitals, totaling 24 hospitals, the most cases being degenerative diseases, namely Hypertension (112,583 cases) and Diabetes Mellitus (102,399 cases). The two most common diseases in outpatients at type C hospitals are Hypertension (42,212 cases) and Diabetes Mellitus (35,028 cases) (Healthoffice, 2015).

About 15% of DM patients in the course of their disease will experience complications of diabetic foot wounds and the risk of lower extremity amputation is 15-46 times higher in DM patients compared to people who do not suffer from DM (Yumizone, 2008). Fifty to 75% lower extremity amputations are performed in patients with diabetes. As many as 50% of amputation cases are estimated to be preventable if patients are taught preventive measures to care for their feet and practice them every day (Maryunani, 2015).

WHO estimates that more than 80% of the population still relies on traditional medicine. In fact, many drugs now mimic some or all of the natural molecular structure of plants. Ethnopharmacology has developed the use of medicinal plants for the therapy of Diabetes Mellitus because it is low cost, easy to obtain, and has few side effects (Aini et al., 2011).

One of the traditional medicines that continues to be developed until now is antidiabetic drugs (Pradono, 2011). Medicinal plants are a source of raw materials for drugs in hyperglycemic cases. There are many types of medicinal plant species in the world which are thought to contain antihyperglycemic compounds. One type of medicinal plant that is believed to lower blood glucose levels is aloe vera (Aveonita, 2015; Pradono, 2011). It is thought that giving aloe vera can protect and restore the function of damaged pancreatic beta cells. Then the content of aloe vera can also work like insulin, and lower blood glucose levels even though all pancreatic beta cells have degenerated (Aveonita, 2015).

Aloe vera contains chemicals that are hypoglycemic, namely chromium and alprogen (Aveonita, 2015; Muliawan, 2019). It is suspected that this chromium functions to stimulate insulin secretion by pancreatic beta cells. This chromium will help insulin work by helping receptor cells to bind to the insulin hormone (Aveonita, 2015). Chromium can increase serotonin which plays a role in increasing the use of glucose by muscles, and a new study shows serotonin has an effect on insulin secretion. Another effect of chromium is to improve insulin resistance by binding to insulin receptors, then chromium will increase the activity of tyrosine kinase, IRS-1 (Insulin Receptor Substrate-1). This condition will increase GLUT 4 activity in binding glucose to be used as energy (Muliawan, 2019).

Antioxidants are substances that the body needs to neutralize free radicals and prevent the damage caused by free radicals to normal cells. People with diabetes are very easy to experience oxidative stress and continue to cause complications of diabetes. The role of flavonoids in this case is to influence the continuous damage to the islets of Langerhans cells in the pancreas so that pancreatic beta cells can regenerate and secrete insulin back into the blood and can restore the sensitivity of the insulin receptor cells by closing and inhibiting K+ channels in the blood. beta cells that stimulate insulin secretion. This condition causes a decrease in blood glucose levels (Nahar & Sarker, 2009).

Diabetes mellitus is a metabolic disorder that interferes with glucose metabolism and has a negative impact on lipid and protein metabolism. This disorder is associated with an increased risk of heart disease. In diabetic patients, the risk of heart disease is 4-5 times greater than in non-diabetic patients. Lipid dysfunction such as increased levels of total cholesterol (TC), low density lipoprotein cholesterol (LDL), triglycerides (TG) and decreased high density lipoprotein cholesterol (HDL) are important risk factors for diabetics. therefore, monitoring of lipid disturbances in these patients is important (Hosseini et al., 2020).

In previous studies, flavonoids are thought to have antidiabetic effects. Flavonoids are found in Aloe vera which are thought to have an antidiabetic effect, but the mechanism of reducing blood glucose levels in the administration of aloe vera extract is not yet clear.

METHOD

The study method was pure experiment (True Experiment). The strategy used is the Pre-Post Test Control Group Design system. The experiment was carried out using Streptozotocin-induced rats which were divided into 4 groups, namely a negative control group for diabetes mellitus with a placebo, treatment group 1 with a dose of aloe vera extract 250 mg/kgBW, treatment group 2 with a dose of aloe vera extract 350 mg/kgBW, treatment group 3 with a dose of aloe vera extract 1000 mg/kgBW.

The population in this study were wistar rats. The number of samples was 20 rats which were divided into 4 groups. The inclusion criteria of the study included 2-3 months of age, male sex, body weight between 150-250 grams, healthy condition characterized by active movement, smooth, shiny and clean fur, thick fur and no significant hair loss, sturdy body not thin, no mucus, pus or blood from the eyes or ears, not too much saliva, no diarrhea and calm breathing. The exclusion criteria for this study included inactive rat movement, rats did not want to eat and drink, rats died during the study, rats had infected wounds which were marked by the presence of pus, excessive exudate before acclimatization, rats had wounds that could be due to bites, or other sharp objects before acclimatization. The independent variable of this study was aloe vera extract, while the dependent variable of this study was blood glucose levels.

The animals used were Wistar rats, male, healthy and have normal activities, 2-3 months old, body weight between 150-250 grams. The experimental animals were obtained from the Animal Experiment shop at the address for Perum Bumi, Mondoroko Raya, Block G02-54 Singosari, Malang Regency. The rats used will be subject to animal health checks at the Malang City Food and Agriculture Security Service. The aloe vera extract material came from Batu City, Malang, East Java and then brought to Materia Medica Batu for the maceration process of aloe vera extract.

Streptozotocin injection was carried out on day 8 after the rats had completed the acclimatization for 7 days. Calculation of the dose of streptozotocin in study rats used a dose of 45 mg/KgBW which was injected intraperitoneally. This Streptozotocin injection will be carried out by a professional laboratory officer at the Experimental Animal Research Laboratory. If the rat's body weight is 200 grams, the calculation of the Streptozotocin dose is 200 grams/1000 grams x 45mg, which is 9 mg. Streptozotocin will be dissolved in 0.1 M citrate buffer pH 4.5 because streptozotocin is insoluble in water. The concentration of STZ made was 22.5 mg/ml. The citrate buffer itself is made from a mixture of citric acid and sodium citrate, then aquabides are added. The mixture was homogenized for 5 minutes, and after homogenizing the mixture was added streptozotocin and homogenized again, then injected intraperitoneally into rat. Citrate buffer volume = 9 mg STZ divided by 22.5 mg/ml = 0.4 ml.

The study was conducted at the Experimental Animal Research Laboratory of Poltekkes Kemenkes Malang in June – September 2021. The rat will be divided into 4 groups where each group consists of 7 rats. But in its implementation, there are 8 dead rats. Rats that have just come to the laboratory will be adapted to the new environment for 7 days. Rats that have adapted will be injected with Streptozotocin on the 8th day so that the rat become diabetic (random blood glucose levels > 200 mg/dl). On the 10th day accompanied by measurements of random blood glucose and cholesterol rats (Pretest) on the 10th day. If it has not become DM then streptozotocin will be re-injected. On the 11th day treatment was given in the form of aloe vera extract until the 19th day, then random blood glucose and cholesterol measurements were taken in rats (Posttest) on the 19th day.

The data analysis technique used Paired T-Test to determine the differences in the pre and post

groups and continued with the Independent Samples T-Test test to test different groups, using a 95% confidence interval or 5% error rate. In addition, multivariate analysis will be carried out using the ANOVA test. In this study, the data analyzed were data from the dependent variable, namely blood glucose levels.

RESULT

Table 1: Characteristics of Rat Body Weight after Streptozotocin induction

	Rat Weight			
	Control Group	Treatment group 1	Treatment group 2	Treatment group 3
Mean	195	165	200	177
Median	202	162	187	177
Min	165	155	165	160
Max	225	180	250	195
Total	6	4	6	4

Table 1 describes the body weight characteristics of streptozotocin-induced rats, the average weight is 165-200 grams. The smallest body weight was in treatment group 1, which was 155 grams, while the highest body weight in group 2 was 250 grams. The number of rats in this study were 20 rats.

Table 2: Characteristics of Streptozotocin-induced rat blood sugar before intervention

	Blood Sugar Before Intervention			
	Control Group	Treatment group 1	Treatment group 2	Treatment group 3
Mean	437	458	423	431
Median	440	486	444	472
Min	350	368	208	265
Max	537	494	600	515
Total	6	4	6	4

Table 2 it can be illustrated that the smallest average blood glucose level before the intervention was in treatment group 2, which was 423 mg/dl, while the highest blood glucose level was in group 1, which was 458 mg/dl. The lowest blood glucose level was in treatment group 2, which was 208 mg/dl, while the highest blood glucose level was in group 2, which was 600 mg/dl.

Table 3: Characteristics of Streptozotocin-induced rat blood sugar after intervention

	Blood Sugar After Intervention			
	Control Group	Treatment group 1	Treatment group 2	Treatment group 3
Mean	464	409	291	382
Median	450	403	281	432
Min	323	379	132	189
Max	616	452	454	477
Total	6	4	6	4

Table 3 it can be illustrated that the smallest average blood glucose level after the intervention was in the treatment group 2, which was 291 mg/dl, while the highest blood glucose level was in the control group, which was 464 mg/dl. The lowest blood glucose level was found in treatment group 2, namely 132 mg/dl, while the highest blood glucose level was in the control group, which was 616 mg/dl.

Table 4: Results of Paired t Test of Blood Glucose Levels in Streptozotocin-Induced Rats

Variable	Paired t Test		
	t	df	Sig. (2-tailed)
Pre-Test and Post Test Control Group	-.783	5	.469
Pre-Test and Post Test in Treatment Group 1	1.596	3	.209
Pre-Test and Post Test in Treatment Group 2	3.276	5	.022
Pre-Test and Post Test in Treatment Group 2	.459	3	.677

Table 4 it can be illustrated that the results of the analysis test between the variables of blood glucose levels before and after being given intervention in treatment group 2 showed a p value of 0.022 which means that there was an effect of aloe vera extract at a dose of 350 mg/kgBW on blood glucose levels in rats induced by Streptozotocin. The control group, treatment group 1 and treatment group 2 did not have a significant difference between before and after the intervention was given.

Table 5: Results of ANOVA Test on Blood Glucose Levels in Streptozotocin-Induced Rats After Intervention

Variable	Variable	ANOVA	Homogeneity Test	Between Groups
Control Group	Treatment group 1	0.85	P Value levane test = 0.154	Sig. = 0.078
	Treatment group 2	0.05		

	Treatment group 3	0.64
Treatment group 1	Control Group	0.85
	Treatment group 2	0.34
	Treatment group 3	0.98
Treatment group 2	Control Group	0.05
	Treatment group 1	0.34
	Treatment group 3	0.55
Treatment group 3	Control Group	0.64
	Treatment group 1	0.98
	Treatment group 2	0.55

Table 5 shows the significance level of the Levene test of 0.078 > 0.05, which means that the four blood glucose groups are the same or homogeneous. The test results of the four groups also had the same average blood glucose as evidenced by a significance value of 0.154 > 0.05. The significance of ANOVA results showed that treatment group 2 had the most effective effect in reducing blood glucose levels in rats induced by Streptozotocin as evidenced by p value 0.05.

DISCUSSION

DM is a chronic metabolic disorder disease characterized by hyperglycemia arising from absolute or relative insulin deficiency (Aveonita, 2015; Pradono, 2011). Type 2 diabetes hyperglycemia is caused by cellular insensitivity to insulin. In addition, insulin secretion defects occur, namely the inability of the pancreas to produce sufficient insulin to maintain normal plasma glucose (Corwin, 2009). Many complications can occur due to hyperglycemia such as hypertension, neuropathy, coronary heart disease, nephropathy, and gangren (Aveonita, 2015).

In hyperglycemic conditions, glucose will undergo a non-enzymatic glycosylation reaction spontaneously with hemoglobin to form glycated hemoglobin. Glucose can be oxidized before binding to hemoglobin as well as glucose after binding to hemoglobin will be oxidized and produce Reactive Oxygen Species (ROS). ROS will increase the expression of Tumor necrosis factor (TNFα) which causes insulin resistance through decreased autophosphorylation of insulin receptors, changes in insulin receptor substrate (IR-s) to inhibitors of receptor tyrosine kinase activity, decreased insulin-sensitive glucose transporter (GLUT-4), alter the function of cells, and increase the circulation of fatty acids. The antioxidant activity of aloe vera extract increases glucose tolerance by preventing blood glucose oxidation, reducing the potential of enzymes that play a role in the transfer of phosphate groups on glucose which is the initial stage of the glycosylation process and improving oxidative stress (Pertiwi & Rahayuningsih, 2012).

The hormone insulin produced by pancreatic beta cells is the key in opening the entrance of glucose in the blood to the cells. This insulin hormone will deliver glucose in the blood so that it can enter the nucleus in the cell with the help of GLUT 4 which is on the cell membrane. The next process, glucose in the cells will be metabolized into ATP. If the insulin hormone is not produced or the amount of insulin hormone in the blood is small, then the glucose in the blood is unable to enter the cells so that it will continue to be in the bloodstream, resulting in a state of hyperglycemia (Aveonita, 2015).

Treatment management in diabetes mellitus consists of non-pharmacological management and pharmacological therapy. Non-pharmacological management can be weight control, diet, and physical activity therapy. Pharmacological management can be in the form of insulin therapy and oral hypoglycemic drugs. People with type 2 diabetes mellitus, the pancreas still produces sufficient amounts of insulin, but the insulin cannot work optimally to bring glucose into the cells due to high cholesterol and triglyceride levels in obese people (Arif, 2020).

One of the traditional medicines that continues to be developed until now is antidiabetic drugs (Pradono, 2011). Medicinal plants are a source of raw materials for drugs in hyperglycemic cases. There are many types of medicinal plant species in the world which are thought to contain antihyperglycemic compounds. One type of medicinal plant that is believed to lower blood glucose levels is aloe vera (Aveonita, 2015; Pradono, 2011). It is thought that giving aloe vera can protect and restore the function of damaged pancreatic beta cells. Then the content of aloe vera can also work like insulin, and lower blood glucose levels even though all pancreatic beta cells have degenerated (Aveonita, 2015).

Aloe vera contains chemicals that are hypoglycemic, namely chromium and alprogen (Aveonita, 2015; Muliawan, 2019). It is suspected that this chromium functions to stimulate insulin secretion by pancreatic beta cells. This chromium will help insulin work by helping receptor cells to bind to the insulin hormone (Aveonita, 2015). Chromium can increase serotonin which plays a role in increasing the use of glucose by muscles, and a new study shows serotonin has an effect on insulin secretion. Another effect of chromium is to improve insulin resistance by binding to insulin receptors, then chromium will increase the activity of tyrosine kinase, IRS-1 (Insulin Receptor Substrate-1). This condition will increase GLUT 4

activity in binding glucose to be used as energy (Muliawan, 2019).

In a previous study, giving aloe vera for 14 days was shown to reduce hyperglycemic conditions. In the treatment group there was a decrease in GDP levels by 20.38±14.7 (18.92%) mg/dl, while in the control group it was 0.38±11.12 mg/dl. Statistical tests showed differences in the decrease in GDP levels between the treatment group and the control group. There was a significant decrease in GDP levels of 20.38 mg/dl after giving 150 grams of aloe vera juice for 14 days (Pertiwi & Rahayuningsih, 2012).

Putriningtyas' research (2013) explains the effect of boiled water from the tubers of the ant nest plant (Myrmecodia pendens) in regulating blood glucose levels, which is thought to be due to the content of tannins, tocopherols, and flavonoids. The function of flavonoids for the human body is as an antioxidant (Putriningtyas, 2013). Antioxidants are substances that the body needs to neutralize free radicals and prevent the damage caused by free radicals to normal cells. The role of flavonoids in this case is to influence the continuous damage to the islets of Langerhans cells in the pancreas so that pancreatic beta cells can regenerate and secrete insulin back into the blood and can restore the sensitivity of the insulin receptor cells by closing and inhibiting K^+ channels in the blood. beta cells that stimulate insulin secretion. This condition causes a decrease in blood glucose levels (Nahar & Sarker, 2009).

Previous research also explained that there was an effect of giving aloe vera extract on decreasing blood glucose levels. Doses of 250mg/kgBW have a better effect on lowering blood glucose levels. Provision of aloe vera extract which has active substances that are thought to be useful as antidiabetics, namely acemannan, anthraquinone and phytosterol. These active substances are thought to have an effect in lowering blood glucose by increasing GLUT4. GLUT4 located in cell membranes will capture sugar from outside and bring glucose into muscle cells, where skeletal muscle is the largest human organ that is sensitive to insulin, which accounts for 85% of the whole body's glucose uptake and plays an important role in maintaining systemic glucose hemostasis (Wanadiatri, 2018).

Previous studies have shown that moderately high doses of aloe vera (200 mg/kgBW and 300mg/kgBW, respectively) help in reducing blood glucose levels and show a marked reduction in blood glucose levels. High doses of aloe vera show a rapid hypoglycemic effect, so further investigations are needed to confirm the bad or good effects of high doses (Agrawal & Ghosh, 2016).

In this study, there were 3 doses given to streptozotocin-induced rats, namely a dose of 250 mg/KgBW, a dose of 350 mg/kgBW, and a dose of 1000 mg/kgBW. One of the doses that gave the greatest effect was rats who were given a dose of 350 mg/kgBW. This is in accordance with Wanadiatri's research (2018) which explains that in his research on rats given ethanolic extract of aloe vera at a dose of 350 mg/kgBW can reduce blood glucose levels. In addition, the 350 mg/kgBW dose grup showed a significant difference to the normal control group ($p<0.05$) (Wanadiatri, 2018). This is evidenced by the results of multivariate analysis through the ANOVA test which shows the p value of the 350 mg/dl dose has the smallest significance value ($p<0.05$) compared to the control group.

In this study, administration of aloe vera extract to rats induced by streptozotocin was proven to improve blood glucose levels. This can happen because of the large number of chemical compounds in aloe vera that have an anti-hyperglycemic function such as chromium, and alprogens.

Flavonoids, saponins, chromium, alprogens, acemannan, anthraquinones, phytosterols are a class of natural compounds that have many health benefits and are an important part of the human diet. This chemical compound will improve the beta function of the pancreas in producing the hormone insulin. Damage to the islets of Langerhans cells in the pancreas will be inhibited and can regenerate so that insulin secretion returns to normal into the blood and can restore the sensitivity of the insulin receptor cells by closing and inhibiting K+ channels in beta cells which stimulate insulin secretion.

CONCLUSION

There was an effect of aloe vera extract at a dose of 350 mg/kgBW on blood glucose levels in streptozotocin-induced rats. Aloe vera extract at a dose of 350 mg/kgBW has the highest effectiveness compared to a dose of 250 mg/kgBW and 1000 mg/kgBW.

SUGGESTION

For further researchers, it is expected to examine the use of aloe vera extract at a dose of 350 mg/kgBW with different administration times, namely 1 x / day, 2 x / day, and 3 x / day.

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CONFLICTS OF INTEREST

The Authors in this research have no affiliations with or involvement in any organization about any financial interest or non financial interest, conflicts of interest in the manuscript, and other relationships that might lead to a conflict of interest.

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