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EFFECT OF SIGER RICE FROM CASSAVA ON BLOOD GLUCOSE LEVEL AND THE PANCREAS IN MICE INDUCED ALLOXAN

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ABSTRACT

Siger rice is a term to mention the product which resemble grains of rice that is processed by cassava. Siger rice is good to be consumed by diabetic's sufferer, because it has low glycemic index and rich dietary fiber. This research aims to know the effect of giving the siger rice on blood glucose level and the pancreas in mice induced alloxan. This research was conducted using a completely randomized design with 3 repetitions. This research used 27 mice which were divided into 9 groups. Each group consisted of three mice. Each group was fed with a different composition of siger rice. Then, the mice were maintained up to 28 days and given feed and drink *ad libitum*. The data were analyzed with Tuckey and followed by analysis of variance (anova) to obtain prediction error variance and to find out if any differences between treatments. The results from anova were then analyzed using least significant different (LSD) at 5% level. The results showed that giving of siger rice effect to decrease in blood glucose levels of mice. Giving siger rice III with composition siger rice:corn starch (30:35) decreased blood glucose level returned to normal 114.67 mg/dL on day 14 and improved performance of the pancreas.

Key words: alloxan, blood glucose, cassava, pancreas, siger rice

I. INTRODUCTION

Rice is one of the most important crops and a primary food source for more than half of the world's population (Dong et al., 2013). Rice supplying as much as half of calories of the world population (Abbas et al., 2011). Southeast Asia's consumers eat large quantities of rice. Most rice is consumed as fully milled white rice that is steamed or cooked in water and served in a bowl at a meal in the home or at restaurant (Baldwin et al., 2012). However, the population of rice consuming countries continue to grow and it is estimated that we will have to produce 40% more rice in 2030 (Khus, 2005).

Dependence on rice as a staple food of Indonesia is not matched by domestic rice production. From Indonesia statistic data in 2010, rice consumption achieves 34 million tones per year. In 2011, Indonesia imported 2.75 million tones (BPS, 2013). In 2019-2021 Indonesia will deficit 3,009 million tones of rices (Abdullah and Adhana, 2011). It proves that Indonesia does not have national food endurance. An effort is needed to supply food needs, thus reaching a solution which is food diversification. But the culture of Indonesian people who consume rice three times a day can be difficult to be changed. So an alternative food that resembeles rice as the main food is needed and contain almost the same nutrition as paddy rice. Siger rice is one of the alternatives that can be developed to substitute the paddy rice.

Siger rice is artificial rice that is produced from cassava with extruder method. Siger rice is made from cassava flour by mixing materials with adding 50% water to the mixture to form clumps, granulating mixture into rice using a extruder with single screw, evaporating grains for 24 hours at temperature of 60 °C and drying until the moisture content reaches below 10%. Siger rice product can be cooked using a minimal amount of water with one time the volume of rice.

Siger rice contains high carbohydrates. There is a considerable variation in bioavailability of carbohydrates among different foods though a higher percentage of carbohydrates in most human diet which is digested and absorbed in the small intestine. It has been suggested that diets containing large amounts of rapidly digestible carbohydrates may be elevate glucose level in blood, which is crucial for diabetics (Jenkins *et al.* 1988). Glycemic index (GI) has been developed for classification of foods containing carbohydrates, which provides quantitatively comparing the blood glucose responses following ingestion of equivalent amounts of digestible carbohydrates from different foods. It has been suggested that low GI foods have beneficial effects in the management of diabetes and high GI foods are crucial as they rapidly elevate glucose concentration in blood (Jenkins et al., 2008; Brouns et al., 2005).

Studies have shown that the digestibility of starch is partly attributed to the inherent properties of starch including crystallinity, granular structure, and amylose:amylopectin ratio. Therefore, the type of crop and variant process play an important role in determining the rate of digestion of their starch (Paes et al., 2008). This study was aimed to determine the effect of siger rice on blood glucose level and the pancreas in diabetic mice induced by alloxan.

II. METHODOLOGY

2.1. Method

This study was conducted in a completely randomized design with 3 replications. The study was conducted using 27 mice (*Mus musculus*) (strain BALB/C, male, 24 days old, weight 19-23 g) obtained from Lampung veterinary Medical Center. Mice were divided into 9 groups. Each group consisted of three mice. Each group was fed with different compositions of siger rice. Mice maintained up to 28 days and were given feed and drink *ad libitum*. The data were analyzed with Tuckey and followed by analysis of variance (anova) to obtain prediction error variance and to find out if any differences between treatments. The results from anova were then analyzed using least significant different (LSD) at 5% level.

2.2. Preparation of Cassava Flour

Cassava (variety of manggu, 8 months) was obtained from Way Kandis – Bandar Lampung. Cassava was peeled its skin and cleaned using water to remove impurities. The clean cassava was then sliced and soaked in water for 72 hours. Every day the water for soaking cassava was changed with clean water. After soaking, the cassava was dried in oven at 60 °C for 1-2 days. The dried cassava was grounded by using a grinding machine and sieved with the size of 60 mesh to get cassava flour. The cassava four was then processed into siger rice. Preparation of cassava flour can be seen in Figure 1.

Figure 1. Preparation of cassava flour

2.3. Preparation of Siger Rice

Cassava flour 1 kg was mixed with 250 mL of water. The mixed cassava was steamed with a temperature of 90 °C for 5 minutes. The gelatinized cassava flour was then subjected to extruder (temperature 80°C, RPM screw 2000, speed 10 kg/h) to form grains. The grains of siger rice were then dried in an oven (memmert) at a temperature 60°C for 24 hours. Siger rice obtained was tested in animal experiments. Preparation of siger rice can be seen in Figure 2.

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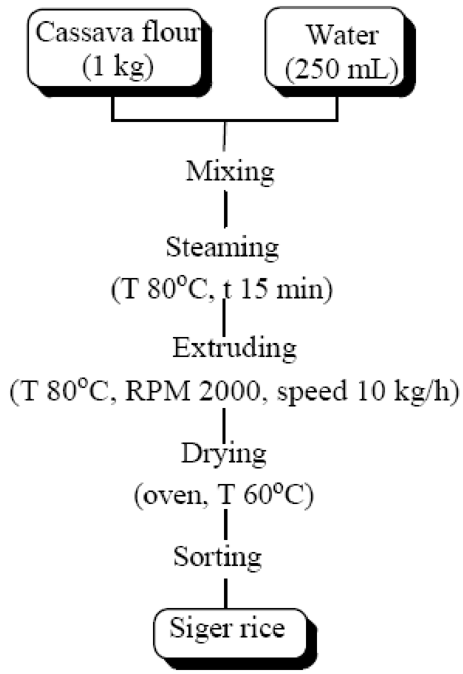

Figure 2. Flow chart of siger rice production

2.4. Introduction of Alloxan Dose

Preliminary test was conducted to establish the effectiveness of a dose of alloxan in inducing diabetic mice. Furthermore, mice were randomly divided into 4 groups with each treatment as shown in Table 1.

Table 1. Distribution of the preliminary test of alloxan dose

No	Groups	Number of mice	Treatment
1	Alloxan dose -1	3	Alloxan dose 140 mg/kg bw
2	Alloxan dose -2	3	Alloxan dose 160 mg/kg bw
3	Alloxan dose -3	3	Alloxan dose 180 mg/kg bw
4	Alloxan dose -4	3	Alloxan dose 200 mg/kg bw

Mice (*Mus musculus*) (strain BALB/C, male, 24 days old, weight 19-23 g, and non-diabetic mice) obtained from Lampung Veterinary Medical Center were adapted for 3 days in the animal laboratory testing in the Department of Agricultural Product Technology, Faculty of Agriculture, Lampung University. Each mouse was given feed and drink *ad libitum*. After the mice were adapted for 3 days, all mice were tested for their blood glucose level. Then the mice were given appropriate treatment in Table 1. After the treatment, the mice were given feed and drink *ad libitum*. On day 7, blood glucose levels were observed. Effective dose causing hyperglycemia (high blood glucose) but does not cause the death of mice was selected for the primary research.

2.5. Siger Rice Feeding Experiment

In the current study used 3 control groups, namely normal control, negative control and positive control and six groups of treatment with siger rice different composition. Normal control was done to determine blood glucose levels in non-diabetic mice and given a standard feed. Negative control was done to determine blood glucose levels in diabetic mice and given standard feed. Positive control was done to determine blood glucose levels in diabetic mice and given drug of glibenclamide and standard feed. While, siger rice groups were done to determine the effect of siger rice in decreasing blood glucose levels and performance of the pancreas in mice. Each group consisted of 3 mice. Determination of the number of test animals and division treatment group are presented in Table 2. While, the siger rice composition can be seen in Table 3.

Table 2. Determination of the number of test animals and division treatment group

No	Group	Number of mice	Treatment
1	Normal control	3	Healthy mice + standard feed
2	Negative control	3	Diabetic mice + standard feed
3	Positive control	3	Diabetic mice + glibenclamide 4,5 mg/kg bw + standard feed
4	Siger rice Composition I	3	Diabetic mice + Siger rice Composition I
5	Siger rice Composition II	3	Diabetic mice + Siger rice Composition II
6	Siger rice Composition III	3	Diabetic mice + Siger rice Composition III
7	Siger rice Composition IV	3	Diabetic mice + Siger rice Composition IV
8	Siger rice Composition V	3	Diabetic mice + Siger rice Composition V
9	Siger rice Composition VI	3	Diabetic mice + Siger rice Composition VI

Table 3. Various compositions of siger rice as feed mice

Composition	Treatment						
(g/100 g)	Standard	I	II	III	IV	V	VI
Corn	65	55	45	35	25	15	5
Siger rice	0	10	20	30	40	50	60
Casein	20	20	20	20	20	20	20
Soybean oil	9	9	9	9	9	9	9
Mineral mix	4	4	4	4	4	4	4
Vitamin mix	2	2	2	2	2	2	2
Total	100	100	100	100	100	100	100

The blood was taken via the tail vein and blood glucose levels measured using glucose meter (accu-chek). A drop of blood from the tail vein is checked by touching and holding the test strip opening to the drop until it has absorbed enough blood to begin the test. Test result can be seen on the monitor screen of accu-chek. All groups except normal control were given alloxan to make into diabetes. Siger rice was given to mice every day *ad libitum* for 28 days. Measurement of blood glucose levels was done every week on days 1, 7, 14, 21, and 28. After 28 days in experiment, mice were turned off by decapitation. Pancreas of mice were removed and fixed with buffer formalin. The pancreas was made culture preparation for histology test. Implementation research can be seen in Figure 3.

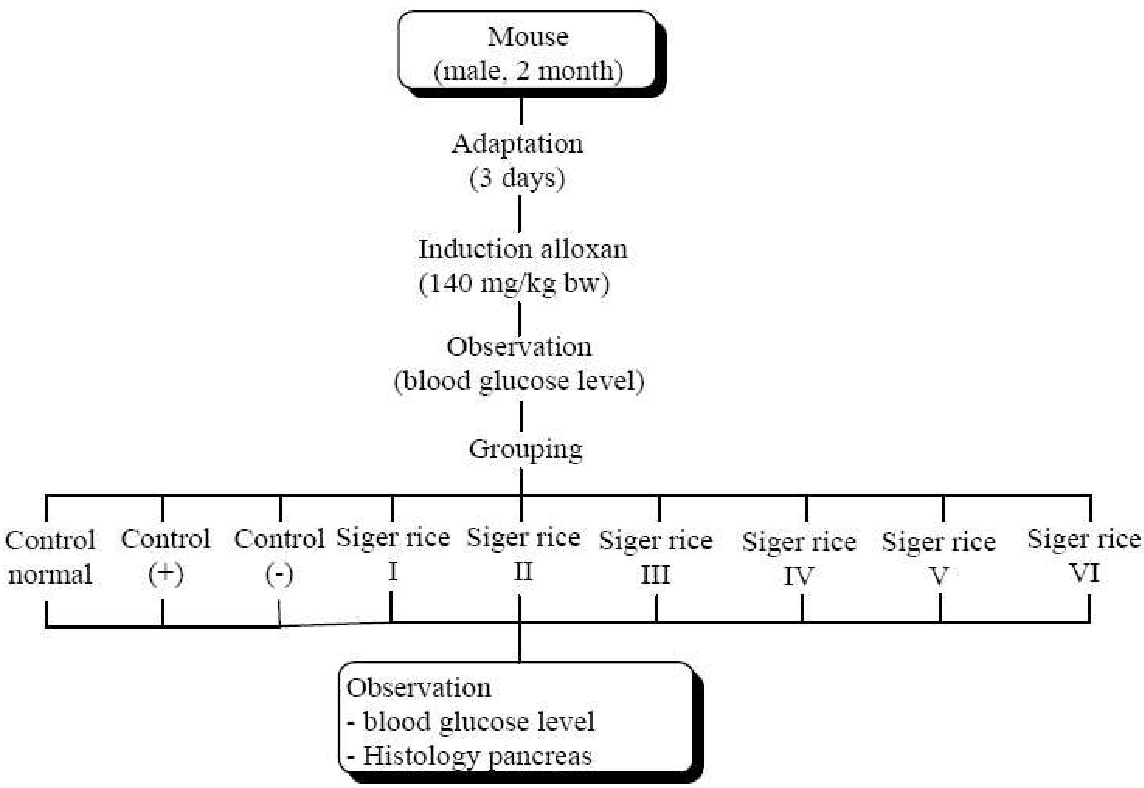

Figure 3. Administration of siger rice in mice induced by alloxan

III. RESULTS AND DISCUSSION

3.1. Introduction of Alloxan Dose

Preliminary test was carried out to determine the effective dose of alloxan that can cause diabetes in mice. The blood glucose levels of the mice after being given various doses of alloxan can be seen in Table 4.

Table 4. Preliminary test of alloxan dose

Alloxan Dose (mg/kg bw)	Blood glucose level (mg/dL)		Number of mice	Number of live mice
	Before induced alloxan	After 7 days induced alloxan		
140	152	307	3	3
160	148	200	3	2
180	145	141	3	1
200	150	-	3	0

180 dose showed two dead rats and live rats with a blood glucose level 5

Based on Table 4 that alloxan dose of 140 mg/kg bw led to three mice have diabetes with blood glucose levels an average of 307.33 mg/dL and no dead mice. A dose of 160 mg/kg bw caused 2 mice have diabetes with an average blood glucose of 200 mg/dL and 1 dead mouse. A doses of 180 mg/kg bw caused 2 dead mice and 1 live mouse with blood glucose level of 141 mg/dL. While, the dose of 200 mg/kg bw caused 3 dead mice. The dose of alloxan to be used in the main study is the dose that causes diabetes in mice but did not cause the death of the mice. A person is said to have diabetes if blood glucose levels greater than 200 mg/dL and fasting blood glucose level higher than 126 mg/dL (FKUI, 2006).

The appropriate dose to induce mice to be diabetic was the dose 140 mg/kg bw with blood glucose levels of 307.33 mg/dL. Administration of alloxan can cause hyperglycemia in mice. Alloxan is one of the substances diabetogenic, especially to the β-Langerhans cells. The compounds of Alloxan enter into β-Langerhans cells and bind to the cell membrane. Alloxan produces free radicals that damage the membrane cells. The presence of free radicals in cells will damage DNA molecules and other cell components and eventually leading to death of the cells (Nugroho, 2006). β-Langerhans cell damage caused the body can not produce insulin and increased blood glucose level (Ali, 1981).

3.2. Antidiabetic Siger Rice

Blood glucose levels of mice before were inducted alloxan between 140-155 mg/dL. One day after being induced alloxan showed blood glucose level in mica between 578,67-597,33 mg/dL. A decrease in blood glucose levels in mice given siger rice treatment can be seen in Figure 4. Results of analysis of variance indicated significant effect between control and mice given siger rice on decreasing blood glucose levels. Further test results of BNT in decline blood glucose levels can be seen in Table 5.

Table 5. Average blood glucose levels in mice at various time of observation

Treatment	Blood glucose level (mg/dL)						Inter-cept	Slope	r2
	Before induced alloxan	After induced alloxan							
		1 day	7 days	14 days	21 days	28 days			
Control	140	108.00b	108,00c	86,33b	88,33c	74,33c	111,2	-1,283	0,881
Control (+)	151	596,33a	430,33a	105,00b	104,67b	103,67c	539,5	-19,12	0,789
Control (-)	147	597,33a	564,67a	419,67a	378,00a	342,67a	605,7	-10,23	0,932
Siger rice I	148	580,67a	384,33a	147,33b	148,33b	187,67b	500,2	-14,82	0,705
Siger rice II	155	583,00a	146,67b	126,00b	125,33b	77,00c	422,1	-14,82	0,581
Siger rice III	146	597,00a	467,00a	114,67b	100,00c	85,33c	561,4	-20,32	0,821
Siger rice IV	152	578,67a	299,67a	64,33b	69,67d	92,67c	468,1	-17,40	0,708
Siger rice V	144	596,00a	273,67a	108,00b	108,67b	109,00c	472,7	-16,45	0,697
Siger rice VI	152	597,33a	448,00a	238,00ab	83,67c	99,00c	576,1	-19,92	0,913

Description: The number followed by the same letters in a row means significantly different at 5% level.

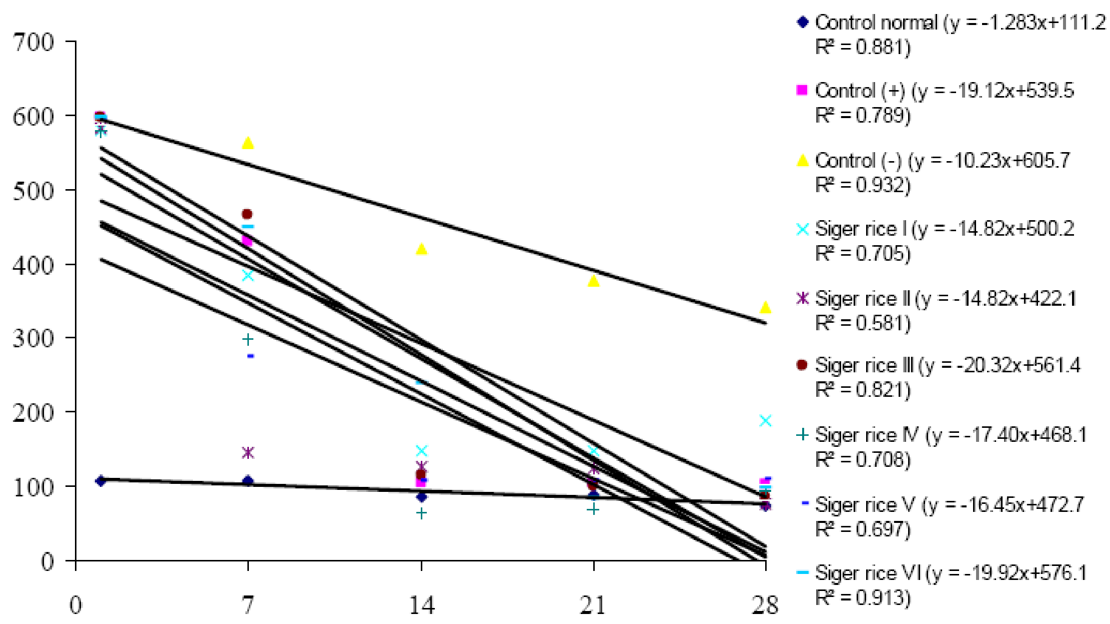

Figure 4. A decrease in blood glucose levels of mice were given rice siger

The results of LSD test on day-1 showed the positive control, negative control, and siger rice I to IV significantly different from control mice. On 7th day showed significantly different from the normal control with the positive control, negative control as well as siger rice I, III, IV, V, and VI, but not significantly different with siger rice II. On the 14th day showed normal control significantly different from the positive control, siger rice I, II, III, IV, and VI, but significantly different from the negative control. On the 21st day showed normal control were significantly different with the negative control and siger rice I,

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but not significantly different from the positive control, siger rice II, III, IV, V, and VI. On the 28th day showed significantly different from normal control, negative control, and siger rice I, but not significantly different from the positive control, siger rice II, III, IV, V, and VI.

Based on the results of measurements of the average blood glucose level in normal control obtained slope of -1.283 which the blood glucose is below 200 mg/dL from day 1 to day 28. The positive control obtained slope of -19.12 where a decline in glucose level from day 1 until 28. A decrease in blood glucose levels to normal occured on the 14th day. This is because the administration of glibenclamide may increase insulin secretion from β-Langerhan cells (Sarfaraz et al., 2012). The negative control obtained slope of -10.23 where blood glucose levels are still high during the time of observation. High levels of blood glucose were caused by administration of alloxan that can inhibite the production of insulin in β-Langerhan cells (Karan et al., 2012).

In the siger rice I obtained slope of -14.82 which occurred a decrease in blood glucose level from day 1 to 28. Decreased glucose levels back to normal occurred on the 14th day. In siger rice II obtained slope of -14.82 where a decline in glucose blood level occurred from day 1 to 28. A decrease in blood glucose levels to normal occurred on the 7th day. In the siger rice III obtained slope of -20.32 where a decline in blood glucose occurred from day 1 to 28. A decrease in blood glucose levels to normal may occur on the 14th day. In the rice siger IV obtained slope of -17.40 where a decrease in blood glucose levels occurred from day 1 to 28. A decrease in blood glucose levels to normal may occur on the 14th day. In the rice siger V obtained slope of -16.45 which a decrease in blood glucose level occurred from day 1 to 28. A decrease in levels of blood glucose occurred on the 14th day. In the siger rice VI obtained slope of -19.92 where a decline in glucose blood levels occurred from day 1 to 28. A decrease in blood glucose levels to normal occurred on the 21st day.

Based on the results of this study indicated that after being induced alloxan had increased blood glucose levels more than 200 mg/dL in mice. Retnaningsih (2001), stated that one day after being induced alloxan showed increasing of blood glucose levels in mice. Alloxan is one of the compound that has capability to inhibit the secretion of insulin from pancreas. A decline blood glucose levels in mice treated by siger rice was observed in each week. The best treatment was composition of siger rice III having slope decrease in blood glucose greater than other composition.

Cassava flour and water having a low glycemic index (GI) of 40,12 (Itam et al., 2012). Glycemic index value categorized into three namely GI low (<55), GI medium (55-70), and high GI (> 70). Factors that affect GI of food include fiber content, comparison amylose and amylopectin, digestibility of starch, fat and protein levels, and processing methods (Gumus et al., 2014).

Cassava flour have crude fiber content of (1.38-3.20%). High crude fiber of food can be used as a functional food to decrease blood glucose level (Janick, 2011). In general, high crude fiber content contributes to a low GI value. Crude fiber improves glycemic response by reducing rate of glucose absorption in small intestine (Cherbut et al., 2004).

The cassava products can be considered good sources of resistant starch (0.56 to 1.1%) which make them beneficial products to the gastrointestinal tract (Pereira dan Leoneh, 2014). The high resistant starch in siger rice supposedly formed during the drying process after steaming. Some studies suggest that resistant starch have significant implications for human health. Resistant starch fraction passes on to the colon, where it is fermented by the microorganisms producing mainly short chain fatty acids. Due to this fact, resistant starch has functional properties and positive effects on diabetes. Resistant starch in siger rice is the most important since their formation is a result of food processing. The amylose content, temperature, physical form, the degree of gelatinization, cooling, and storage affect its contents (Nugent, 2005; Sajilata et al., 2006).

The glycemic index (GI) is an important parameter of food quality which compares the hyperglycaemic effect of a tested meal with pure glucose (Jenkins et al., 2008). The GI is a measure of the food power to raise glucose concentration after a meal. Foods with carbohydrates that break down quickly during digestion and release glucose rapidly into the bloodstream tend to have a high GI. Siger rice with carbohydrates of crude fiber and resistant starch that break down more slowly, releasing glucose more gradually into the bloodstream, tend to have a low GI. A lower glycemic index suggests slower rates of digestion and absorption of the carbohydrates and may also indicate greater extraction from the liver and periphery of the products of carbohydrate digestion (Jenkins et al., 2008; Brouns et al., 2005). A lower glycemic response usually equates to a lower insulin demand and may improve long-term blood glucose control and blood lipids (Atkinson et al., 2008).

3.3. Histology of Pancreas

Analysis of pancreas histological is done to see the damage the pancreas of mice after being given siger rice. According to Lenzen (2008), there are four phases after being induced alloxan. A first transient hypoglycaemic phase of up to 30 min starts within time of alloxan injection. This short-lived hypoglycaemic response is the result of a transient stimulation of insulin secretion, as documented by an increase in the plasma insulin concentration. The underlying mechanism is a temporarily reduced consumption and increased availability of ATP caused by blockade of glucose phosphorylation through glucokinase inhibition. The second phase starts with an increase in the blood glucose concentration, 1 h after administration of the alloxan, and a decrease in plasma insulin. This first hyperglycaemic phase, which usually lasts 2–4 h, is caused by inhibition of insulin secretion leading to hypoinsulinaemia. During this phase the β-Langerhans cells show the following morphological characteristics: intracellular vacuolisation, dilation of the rough endoplasmic reticulum, decreased golgi area, reduced secretory granules, and insulin content, and swollen mitochondria. The third phase, again a hypoglycaemic phase, typically occurs 4–8 h after the injection of the alloxan and lasts several hours. It may be so severe that it causes convulsions, and may even be fatal without glucose administration, in particular when liver glycogen stores are depleted through starvation. This severe transitional hypoglycaemia is produced by the flooding of the circulation with insulin as a result of alloxan-induced secretory granule and cell membrane rupture. Pancreatectomy prevents this phase. In addition to the morphological changes seen in the first phase, the beta cell nuclei are pyknotic.

The fourth phase is the permanent diabetic hyperglycaemic phase. Morphologically, complete degranulation and loss of β-Langerhans cells integrity is seen within 12–48 h. siger rice administration in mice induced by alloxan can improve damaged β-Langerhans cells. Mice with diabetes after being induced alloxan can be seen in Figure 5.

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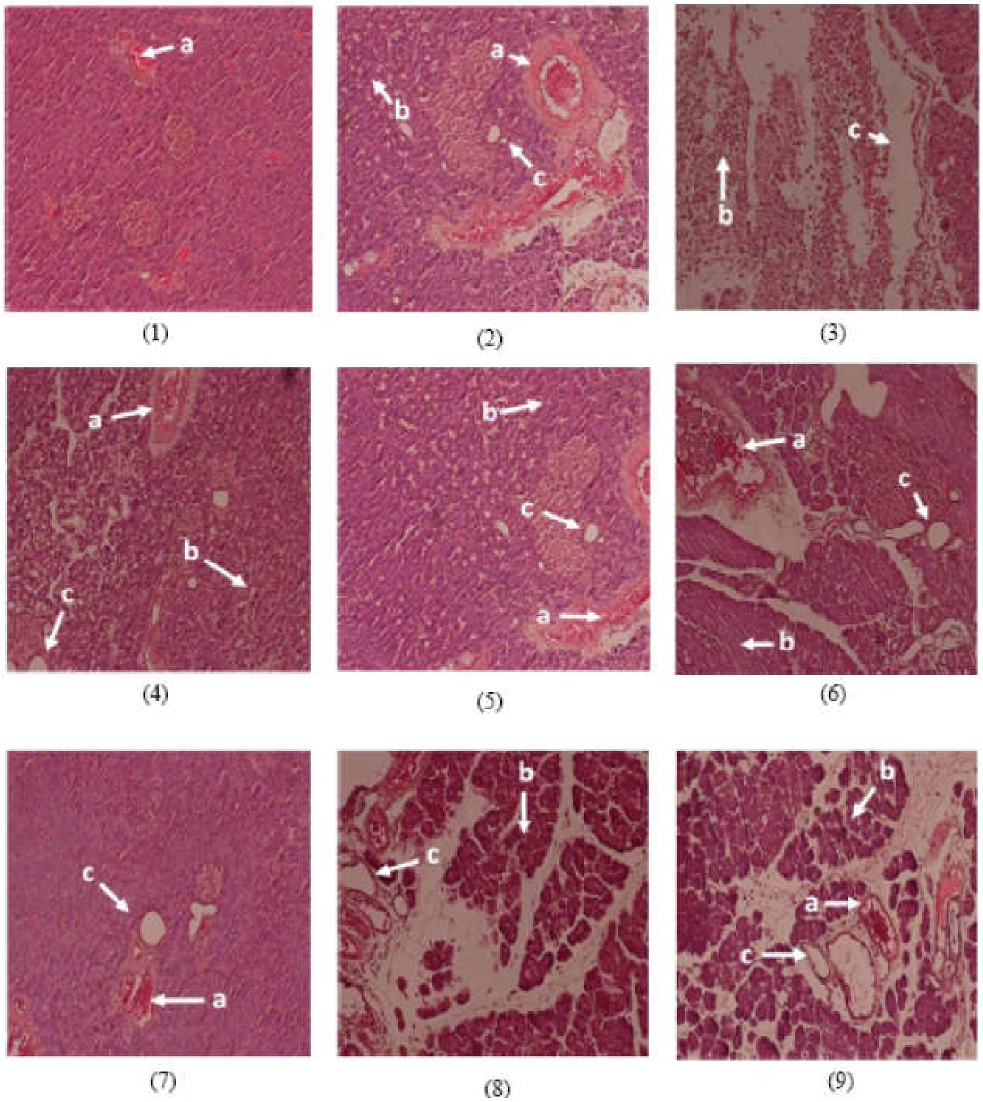

Figure 5. Histology pancreas of mice after 28 days of treatment (1) healty mouse, (2) control positive, (3) control negative, (4) siger rice I, (5) siger rice II, (6) rice siger III, (7) siger rice IV, (8) siger rice V, (9) siger rice VI, (a) bleeding in the β-Langerhans cell, (b) the vacuole in acinier cell, (c) focal nekrosa in β-Langerhans cell

In the normal control indicates the amount of blood and excess mucus in the pancreas, but it did not spoil the β-Langerhans cells and pancreas of mice. For the positive control shows mild bleeding and does not damage the β-Langerhans cells. Treatment of siger rice I to VI indicates the number of blood and excess mucus part of the pancreas, and there are cavities on the walls of the pancreas, but the β-Langerhans cells are not too damaged. In contrast to the negative control treatment showed severe damage on the vacuole in a cell of acinier and focal nekrosa in β-Langerhans cell. Damage to the pancreas of mice is caused by alloxan injection. Alloxan has capability to destroy β-Langerhans cells thereby inhibiting the secretion of insulin.

Mechanism of alloxan on pancreatic damage occurs by the formation of reactive oxygen compounds that form superoxide radicals via the redox cycle. Through a redox cycle will form hydroxyl very reactive which cause damage β-Langerhans cells quickly (Lenzen, 2008). Additionally, alloxan interfere with the oxidation process of cells by expenditure calcium ions from mitochondria resulting in a disruption of homeostasis which causes the death of pancreas cells (Nugroho, 2006).

The majority of islet cells is formed by β-Langerhans cells which are responsible for producing insulin. Depletion of β-Langerhans cells will therefore result in insulin deficiency which will lead to a disorder in carbohydrate metabolism with a resultant hyperglycaemia. In this study, alloxan which selectively destroy β-Langerhans cells of the islet was used to induce diabetes. Insulinitis and loss of β-Langerhans cells were observed which may be seen in diabetes. insulinitis is evidenced by bleeding in the β-Langerhans cell, the vacuole in a cell acinier, and focal nekrosa in β-Langerhans cell in and around the islet. Islet cells of mice treated with siger rice has regenerated considerably suggesting the presence of stable cells in the islets with the ability to cause regeneration of pancreatic β-Langerhans cells. This also suggests that the siger rice has the ability of inducing the quiescent cells to proliferate to replace the lost cells.

The findings of the present study well demonstrated that (1) giving siger rice showed effect to the decrease in blood glucose levels mice. (2 giving siger rice III with composition of siger rice:corn starch (30:35) decreased blood glucose levels returned to normal 114.67 mg/dL on day 14.

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