UNDERGRADUATE THESIS
EFFECTIVITY TEST OF ZALACCA RIND EXTRACT ON BLOOD SUGAR LEVEL OF DIABETIC

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FACULTY OF HEALTH SCIENCE
UNIVERSITY OF DARUSSALAM GONTOR
PONOROGO
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EFFECTIVITY TEST OF ZALACCA RIND EXTRACT ON BLOOD SUGAR LEVEL OF DIABETIC

Submitted to Undergraduated Program University of Darussalam Gontor in Partticial Fulfillment of The Requirements for Health Science

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ABSTRAK

Latar Belakang: Diabetes Mellitus tipe 1 adalah salah satu penyakit tidak menular yang meningkat setiap tahun di Indonesia. Pemanfaatan kulit salak dapat mengurangi kadar gula darah karena mengandung flavonoid. Orang-orang menganggap kulit salak adalah sampah tetapi sebenarnya dapat digunakan sebagai alternatif untuk mengurangi gula darah. **Tujuan**: Untuk mengetahui uji efektivitas ekstrak kulit salak (*Salacca zalacca* [Gaertner] Voss) terhadap kadar gula darah tikus wistar putih diabetes (*Rattus norvegicus L*). **Metode**: Penelitian ini bersifat eksperimental dengan desain kelompok kontrol pre post test. Subjek penelitian adalah tikus wistar yang diberi ekstrak kulit salak untuk intervensi, glibenclamide untuk kontrol positif dan pakan standar untuk kontrol negatif. Analisis statistik menggunakan Shapiro-Wilk untuk uji normalitas, Kruskall-Wallis untuk mengidentifikasi perbedaan antara kelompok dan post hoc oleh Mann Whitney untuk menganalisis setiap kelompok. **Hasil**: Tidak ada perbedaan yang signifikan antara kelompok sig. 0,559 (p> 0,05). Kontrol negatif menunjukkan bahwa kadar gula darah terus berkurang walaupun tidak diberi apa-apa dan hanya pemberian makanan normal. **Kesimpulan**: Penelitian ini mengungkapkan bahwa ekstrak kulit salak dapat mengurangi kadar gula darah pada dosis 0,075 g / 200 gW, 0,15 g / 200 gW dan 0,225 g / 200 gW tetapi tidak signifikan secara statistik.

Kata kunci: kadar gula darah, diabetes, ekstrak kulit salak

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ABSTRACT

Background : Diabetes Mellitus type 1 is one of non communicable diseases which increases every year in Indonesia. Utilization the zalacca rind can reduce blood sugar levels because it contains flavonoids. The people assume the zalacca rind is rubbish but actually can be used as an alternative to reduce blood sugar. **Objective** : To know effectivity test of zalacca (*Salacca zalacca* [Gaertner] Voss) rind extract on blood sugar level of diabetic white wistar rats (*Rattus norvegicus L*). **Method** : The research was experimental with pre post test control group design. The subject was wistar rat given zalacca rind extract for intervention, glibenclamide for positif control and standar feed for negative control. Statistical analysis used Shapiro-Wilk for normality test, Kruskall-Wallis for identification any difference between group and post hoc by Mann Whitney for different among group analysis. **Results** : There was no significant difference between groups sig. 0.559 ($p>0.05$). Negative control showed that blood sugar level continue to reduce even if not given anything and only normal feed. **Conclusion** : The study revealed that the zalacca rind extract can reduce blood sugar level at dosage 0.075 g / 200 gW, 0.15 g / 200 gW and 0.225 g / 200 gW but not statistically significant.

Keyword: *blood sugar level, diabetic, zalacca rind extract*

STATEMENT OF ORIGINALITY

DECLARATION

I hereby,

Name : Chindya Eka Tustyas Putri

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Title : Effectivity Test of Zalacca Rind Extract on Blood Sugar Level of Diabetic

I sincerely declare that this undergraduate thesis originally belongs to my work and not belongs to other researcher for a different degree. Furthermore, the undergraduate thesis is never published before, except for some parts with their original references.

Otherwise, if it found plagiarism, I'm ready to be ceased academically.

Ponorogo, April 6th 2019

Author,

Chindya Eka Tustyas Putri

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UNDERGRADUATE THESIS

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Ponorogo, April 6th 2019

Sincerely Yours,

Chindya Eka Tustyas Putri

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CHAPTER 1

INTRODUCTION

1.1. Background of Research

There has been a shift in the pattern of diseases between communicable diseases and non-communicable diseases, such as diabetes mellitus, cancer, stroke, heart disease, chronic obstructive pulmonary disease (COPD), etc due to lifestyle changes, increasing economics and social status known as epidemiological transitions (Wahyuni *et al*., 2013). Diabetes mellitus is a disorder of homeostatic nutrient that occurs due to pancretic dysfunction or an abnormal response from cells targeted to the hormone insulin (David & Dolores, 2007). People with diabetes mellitus increase from 108 million in 1980 to 422 million in 2014 (WHO, 2016). Global prevalence in 2014, 8,5% of adults aged 18 years and over suffered from diabetes mellitus. In 2016, diabetes mellitus was the direct cause of 1,6 million death and in 2012 high blood glucose was another 2,2 million cause of death (WHO, 2018).

According to the Data and Information Center at 2016 showed that non-communicable diseases were the cause of death in the world which has a percentage of 70% (Profil Kesehatan Indonesia, 2016). According to the ministry of health based on basic health research data for the year 2018 the prevalence of diabetes mellitus in the population aged of ≥15 years in Indonesia was 10.9% (Ministry of Health, 2018).

According to the Ministry of Health's Data and Information Center in 2014, the proportion of diabetes mellitus in Indonesia amounted to 6.9% in the Indonesian population aged 15 years and over which was estimated at 176,689,336 people and 0.6% of Indonesia's population aged 15 years and above or around 1 million people actually feel the symptoms of diabetes mellitus but have not been examined and are confirmed to have diabetes mellitus (Ministry of Health, 2014).

Patients with diabetes mellitus find many effects are not expected, therefore begin to look at alternative medicine by utilizing plants or natural ingredients to reduce blood sugar levels with little or no side effects. Allah has created this realm for humans with various medicinal properties, and this is a gift from Allah SWT that must be utilized and studied as mentioned in Al-Qur'an Surah As-Syu'ara (42) 7-8:

أَوَلَمْ يَرَوْا إِلَى الأَرْضِ كَمْ أَنْبَتْنَا فِيْهَا مِنْ كُلِّ زَوْجٍ كَرِيْمٍ ، إِنَّ فِى ذَالِكَ لَأَيَةً وَمَا كَانَ أَكْثَرُهُمْ مُّؤْمِنِيْنَ

"Do they not look at the earth, how many noble things of all kinds We have produced therein?. Verily, in this is a Sign: but most of them do not believe."

Indonesia's people is currently utilizing many different types of plants as medicine not only to treat various diseases but also to maintain health as well. Types of herbs that are used as medicine are often referred to as herbal medicines. One of the plants that can be used as medicine is zalacca (Haryoto & Priyatno, 2018). Usually many people consume flesh of zalacca fruit and dispose of their rind even though is very nutritious. Zalacca rind is usually used as waste that cannot be used again, but the zalacca rind contains very high nutritional value.

According to Kanon *et al.* (2012) the zalacca rind can reduce blood sugar levels because it contains flavonoids. Pterostillbene is a compound contained in the zalacca rind which acts as an anti-diabetic and reducing blood sugar levels (Sahputra, 2008). According to Kanon *et al.* (2012) zalacca rind extracts have an effect on reducing blood sugar levels of male white wistar rats induced by sucrose. In the research of Suarsana (2009) stated that flavonoids can reduce blood sugar levels in rats by stimulating β-pancreatic cells to produce more insulin. In a study by Widyaningsih and Andrianty (2014) stated that the treatment of administration of herbal tea with the zalacca rind can affect the decrease in blood glucose sugar levels reaching 54.43%. In the research of Evacuasiany *et al.* (2014) stated that the zalacca rind extract reduced blood glucose levels in rats comparable to glibenclamide by Oral Glucose Tolerance Test (OGTT).

The zalacca rind used as an alternative to reduce blood sugar levels. During this time the community is not aware of the content contained in the zalacca rind. The community thinks that the zalacca rind is rubbish but the zalacca rind can be used as an alternative treatment.

1.2. Formulation of the Research Problem

How effectivity test of zalacca (*Salacca zalacca* [Gaertner] Voss) rind extract on blood sugar level of diabetic white wistar rats (*Rattus norvegicus L.*)?

1.3. Objectives Research

1.3.1. General Objective

To know effectivity test of zalacca (*Salacca zalacca* [Gaertner] Voss) rind extract on blood sugar level of diabetic white wistar (*Rattus norvegicus L.*)

1.3.2. Specific Objectives

1. Knowing the effectiveness of zalacca rind extract against blood sugar levels at a dosage of 0.075 g / 200 gW
2. Knowing the effectiveness of zalacca rind extract against blood sugar levels at a dosage of 0.15 g / 200 gW
3. Knowing the effectiveness of zalacca rind extract against blood sugar levels at a dosage of 0.225 g / 200 gW

1.4. Benefits of Research

1.4.1. Benefit for Researchers

Can provide new insights for diabetes researchers to reduce blood sugar levels by utilizing the zalacca rind as an alternative treatment.

1.4.2. Benefit for Institutions

Can provide scientific information that is useful for the development of science. Besides that, it can be a reference for further research.

1.4.3. Benefit for the Community

Providing information to the public about the benefits of zalacca rind extract as an alternative treatment for people with diabetes mellitus.

1.5. Authenticity of the Research

Table 1. Authenticity of the Research

Researchers	Title	Variable	Results	Difference
Kanon, M. Q., Fatimawali dan Widdhi, B (2012)	Effectivity Test of Salacca (*Salacca zalacca* [Gaertn] Voss) Rind Extract on Blood Sugar Level Decrease of White Male Wistar (*Rattus norvegicus L.*) Induced with Sucrose	Independent variable: extract of zalacca rind Dependent variable: blood sugar levels of male white rats	The salacca rind extract has an effect on the decrease in blood sugar levels of male white rats of tourist lines induced by sucrose	Discusses about male white rats induced by sucrose

Researchers	Title	Variable	Results	Difference
Ega Purnamasari, Ega, Eti Yerizel, Efrida (2014)	Effect of Giving Aspartame on Blood Glucose Levels of Alloxan-Induced Diabetes Rats	Independent variable: giving aspartame Dependent variable: blood glucose levels of diabetic diabetes mellitus induced by alloxan	Giving aspartame affects the decrease in blood glucose levels induced by alloxan	Discuss about giving aspartame to rat blood glucose
Endang Evacuasiany, Pinandojo Djojosoewarno, I Putu Gede Darma Eka Putra (2014)	The Effect of Salacca (*Salacca zalacca)* Rind Extract on Blood Sugar Level of White Swiss Webster Male Rats (*Mus musculus*) With Oral Glucose Tolerance Test	Independent variable: extract of the salacca rind Dependent variable: blood sugar levels in rats	The salacca rind extract lowers blood glucose levels in rats comparable to glibenclamide by Oral Glucose Tolerance Test (OGTT)	Discussing about the salacca rind extract extracts lower blood glucose levels with an oral glucose tolerance test

Researchers	Title	Variable	Results	Difference
Muhtadi. Eni Setyowati, Tanti Azizah (2012)	Antidiabetic Activity of Melitus of Sweet Orange Fruit Extract (Citrus sinensis) and Kelengkeng Fruit Rind (Euphoria longan (Lour.) Steud) Against Male White Rats Wistar Line Induced by Alloxan.	Independent variable: extract of sweet orange peel and kelengkeng fruit rind Dependent variable: antidiabetic activity	Sweet orange peel extract and kelengkeng fruit rind can reduce blood glucose levels in diabetic rats induced by alloxan	Discusses about sweet orange peel extract and kelengkeng fruit peel against rats induced by alloxan

CHAPTER 2

LITERATURE REVIEWS

2.1. Diabetes Mellitus

2.1.1. Definition

Diabetes mellitus is a hyperglycemia disease that is characterized by absolute absence of insulin or a decrease in relative cell insensitivity to insulin (Corwin, 2008). More than 240 million people in the world currently have diabetes. This number will continue to grow to more than 380 million by 2025. In some Asian, Middle Eastern, Oceania and Caribbean countries, diabetes 12-20% of the population has diabetes. By 2025, 80% of cases of diabetes will occur in low and middle income countries (Apriyanti, 2012).

Diabetes mellitus type 1 or previously known as insulin dependence experienced by adolescents or childhood is characterized by a lack of insulin production and requires the addition of loyal insulin today. Type 2 diabetes mellitus or previously referred to as non-insulin-dependent insulin resistance occurs in the majority of diabetics worldwide and is largely the result of overweight and lack of physical activity (WHO, 2018). Some oral antidiabetic drugs in the sulfonylurea group have hypoglycemic effects, allergic skin reactions, aplastic anemia, and hemolytic anemia. This hypoglycemia can actually result in patients with shock, seizures, coma and even death (Dipiro *et al*., 2015).

Diabetes mellitus is a metabolic disorder characterized by an increase in blood glucose levels which is associated with abnormal insulin secretions or insulin work from genetic or environmental factors and results in complications (Dipiro *et al*., 2015). Diabetes is a chronic disease that occurs when the pancreas does not produce enough insulin or when the body cannot use insulin that is produced effectively. Insulin is a hormone that regulates blood sugar. Hyperglycemia is the effect of uncontrolled diabetes which causes serious damage to many body systems, especially nerves and blood vessels (WHO, 2018).

Normal blood sugar levels are 4-8 mmol / l or 60 - 140 mg / dL. Everyone has different blood sugar levels, which are influenced by diet, activity intensity, and physical exercise. (Evacuasiany, *et al.*, 2014)

The test used for the diagnosis of diabetes include fasting plasma glucose test (FPG, plasma glucose fasting) and oral glucose tolerance test (OGTT, oral glucose tolerance test). The American Diabetes Association recommends FPG test because it is faster and easier to do, and costs are cheaper than OGTT. FPG levels between 100 - 126 mg / dL is considered prediabetes, and FPG levels of 126 mg / dL or more are considered diabetes. For OGTT, individual blood sugar is measured after fasting and two hours after drinking sweet drinks. Two-hour OGTT between 140 - 199 mg / dL indicates diabetes. The range of prediabetes values allows for early intervention in patients who are at risk of developing diabetes for sure. Early intervention is very important because when diagnosed with type 2 diabetes, 20% of patients have retinal damage, 8% have kidney dysfunction, and 9% have neurological symptoms (Corwin, 2008).

2.1.2. Risk Factors

Risk factors for diabetes mellitus are grouped into two groups, there are modifiable risk factors and non-modifiable factors. Modifiable risk factors are related to unhealthy behavior, such as excessive weight, abdominal / central obesity, lack of physical activity, hypertension, dyslipidemia, unhealthy diet, abnormal blood sugar history, and smoking. Risk factors that cannot be modified, such as race and ethnicity, age, sex, family history of diabetes mellitus, childbirth history of low-weight babies less than 2500 grams, childbirth history of body weight more than 4000 grams (Ministry of Health, 2014).

2.1.3. Sign and Symptom

Diabetes mellitus often appears asymptomatic, but there are some symptoms to watch out for the possibility of suffering from diabetes mellitus. In type 1 diabetes mellitus the common symptoms are polyuria, polyphagia, polydipsia, unwanted weight loss, fatigue, irritability, and pruritus (itching of the skin), while there are almost no common symptoms in people with type 2 diabetes. Common symptoms suffered by people with type 2 diabetes mellitus appear unnoticed and treatment began several years later when the disease had developed. Patients with type 2 diabetes mellitus are more prone to infection, hyperlipidemia, difficulty recovering from injury, obesity, and complications in blood vessels and nerves (Directorate of Pharmacy Development, 2005).

2.1.4. Pathophysiology

Patients with type 1 diabetes mostly occurs in people under 30 years. That is why this disease is often dubbed diabetes in children because sufferers are more common in children and adolescents. In type 1 diabetes, the pancreas cannot produce enough insulin due to abnormalities of the body's immune system that destroy cells that produce insulin or because of viral infections so that the hormone insulin in the body decreases and causes sugar deposits in the bloodstream (Apriyanti, 2012).

Disorders of insulin production in type 1 diabetes mellitus occur due to Langerhans β cell damage caused by an autoimmune reaction. Autoimmune destruction of Langerhans β cells in the pancreatic gland directly results in deficiency of insulin secretion (Directorate of Pharmacy Development, 2005).

Type 2 diabetes mellitus is caused by insulin target cells unable to respond to insulin normally, which is called insulin resistance. Besides the impaired insulin secretion and hepatic glucose production were excessive but not β Langerhans cell damage in autoimmune

(Directorate of Pharmacy, 2005).

2.1.5. Drugs

Drug therapy for diabetes mellitus to do with the form of an oral hypoglycemic drug therapy, insulin therapy or a combination of both. Insulin therapy is a must for people with type 1 diabetes mellitus for β Langerhans cells of the pancreas gland is damaged and therefore can not produce insulin, it must receive exogenous insulin to help metabolize carbohydrates running normally in the body (Directorate of Pharmacy, 2005).

Oral hypoglycemic drugs are intended for patients with type 2 diabetes mellitus. The classification of oral hypoglycemic drugs based on their working mechanism is divided into three groups: drugs that increase insulin secretion (oral hypoglycemic drugs in sulfonylureas and glinides, insulin sensitisers (biguanide and thiazolidindion hypoglycemic drugs) and carbohydrate catabolism inhibitors (α-glucosidase inhibitors also called “starch-blockers”) (Directorate of Pharmacy, 2005).

2.1.6. Diet

The nutritional requirements to prevent diabetes mellitus is actually almost the same as an ordinary person, so do not need special food. But what must be considered is some food choices, especially carbohydrates (Segal *et al*., 2018).

Diet is an attempt to control diabetes mellitus. The key is to choose the right carbohydrate. The right carbohydrates for people with diabetes mellitus are those that contain complex carbohydrates, which can release blood glucose gradually so there is no increase in blood sugar levels after a sudden meal (Evert, 2014)

Complex carbohydrates in the body must be parsed into a single chain before they are absorbed into the blood, while simple carbohydrates directly into the blood so that blood sugar levels can rise quickly. Complex carbohydrates such as rice or fibrous bread, while simple carbohydrates such as sugar, ice cream, sugary soft drinks, syrup, and sweets (Almatsier, 2004).

Dietary patterns of diabetics must be adjusted. Reducing calorie intake will reduce blood sugar levels, but lack of sugar can be dangerous. Exercise is one of the appropriate ways to control diabetes because exercising can make insulin work more effectively. The recommended sports are CRIPE (Continuous, Rhytmical, Interval, Progressive, Endurance Training) (Directorate of Pharmacy Development, 2005).

2.1.7. Type of Diabetes Mellitus

2.1.7.1. Diabetes Mellitus Type 1

Type 1 diabetes mellitus is hyperglycemia due to the absolute absence of insulin. Previously, this type of diabetes was referred to as insulin dependent diabetes mellitus (IDDM), because individuals with this disease had to receive replacement insulin (Corwin, 2008).

The pancreas is difficult to produce insulin, so insulin must increase every day. Generally by injecting insulin. Giving is not given orally because insulin can be destroyed in the stomach when inserted through the mouth. Another way is to improve the function of the pancreas. If the pancreas can return to function normally, the pancreas can meet the insulin needs of the body (Apriyanti, 2012).

2.1.7.2. Diabetes Mellitus Type 2

Hyperglycemia caused by cellular insensitivity to insulin is called type 2 diabetes mellitus. In addition, there is a defect in insulin secretion inability of the pancreas to produce enough insulin to maintain normal glucose. Although insulin levels may decrease slightly or be in the normal range, the amount of insulin remains low so that glucose levels increase. Because insulin is still produced by pancreatic beta cells, not insulin dependent or NIDDM (Non

Insulin Dependent Diabetes Melitus), it is actually not appropriate because many individuals who suffer from type 2 diabetes mellitus can be treated with insulin (Corwin, 2008).

The cause of type 2 diabetes is that insulin produced by the pancreas is insufficient to bind the sugar in the blood due to an unhealthy diet or lifestyle. Treatment of type 2 diabetes is by forcing the work function of the pancreas so that it can produce more insulin. If the pancreas can produce insulin that is needed by the body, the blood sugar level will decrease because it can be converted into energy (Apriyanti, 2012).

2.2. Zalacca (*Salacca zalacca* (Gaertner.) Voss)

Zalacca is a species of palm tree (family Arecaceae) native to Java and Sumatra in Indonesia, and also cultivated in other areas as food crops, and reportedly naturalized in Bali, Lombok, Timor, Maluku, and Sulawesi (Ashari, 2013).

This plant is a plant that has a very large thorn in the stem, and even around the fruit. There are several species of zalacca that are widespread, but only a few are known. The classification and morphology of zalacca plants are as follows:

Divisi : Spermatophyta

Sub divisi : Angiospermae

Class : Monocotyledoneae

Ordo : Principes

Familia : Palmae

Genus : *‘Salacca*

Species : *Salacca zalacca* **(Gaertner.) Voss** (Steenis, 1975; Tjitrosoepomo, 1988)

The fruit in this plant is rather ovoid triangular turned, pointed at the base and rounded at the end, 1.5 - 10 cm long, which is encased by scales that almost resembles a shiny black-brown snake, there are fine thorns that protect it (Suskendriyati *et al.*, 2000).

Figure 1. Zalacca *Pondoh*

Source: Indonetwork (2017)

Zalacca used is a type of *pondoh* rind. Zalacca *pondoh* is popular because it tastes sweet, can be accepted by consumers, therefore many consumers consume it by removing the rind because of ignorance of the benefits of zalacca rind itself.

In the research of Sahputra (2008), the results of phytochemical tests showed that the extracts of rind and flesh of zalacca contained flavonoids, which can inhibit the activity of α-glucosidase and α-amylase enzymes. Glycogen degradation involves the α-glucosidase enzyme in the catabolic process of polysaccharides. If the α-glucosidase enzyme can be inhibited, the catabolism of polysaccharides can be inhibited as well so that it can reduce blood sugar levels in diabetics.

In herbal teas, the zalacca rind contains antioxidant activity, total phenol values, and flavonoids (Anjani *et al.*, 2015). Phenol acts as a secondary antioxidant as a therapy for type 2 DM, which functions to reduce blood sugar levels. People with diabetes mellitus will increase the incidence of oxidative stress which can trigger microvascular complications (nephropathy, neuropathy, and retinopathy). A source of antioxidants is a food source that is needed by people with diabetes mellitus as a secondary antioxidant that can help the work of primary antioxidants by inhibiting oxidative stress (Isdamayani & Panunggal, 2015).

2.3. Wistar Rats (*Rattus norvegicus L.*)

Wistar rats (*Rattus norvegicus L.*) or also called Norwegian rat is one of the animals commonly used in experimental laboratories. Taxonomy of white rats (*Rattus norvegicus L.*) is as follows:

Kingdom : Animalia

Phylum: Chordata

Class : Mammals

Ordo : Rodentia

Subordo : Odontoceti

Family : Muridae

Genus : *Rattus*

Species: *Rattus norvegicus L.* (Wulangi, 1999)

Figure 2. Wistar Rat

Source: Estina (2010)

Rats have properties that distinguish them from other experimental animals is that rats cannot vomit. This is because an unusual anatomical structure in the place of the esophagus empties into the stomach and does not have a gallbladder (Smith & Mangkoewidjojo, 1998). In addition, white rats have the advantage of being a model that reflects the functional character of mammalian body systems (Krinke, 2000).

Wistar rats are outbred strain from albino rats belonging to the species Rattus novergicus. This strain was developed at the Wistar Institute in 1906 for use in biological and medical research, especially rat strains were mainly developed to serve as models of organisms when laboratories were mainly used in public house rats. More than half of all strains of laboratory are descended from native colonies founded by physiologists Henry Donaldson, J. Milton scientific administrator Greenman, and genetic researcher or embryologist Helen Dean Raja.

Rats as omnivorous animals usually want to consume all foods that humans can eat. Feed requirements for a rats every day are approximately 10% of body weight, if the feed is in the form of dry feed. This can also be increased to 15% of body weight if the feed consumed is in the form of wet food. Daily drinking needs of rats is about 15-30 ml of water. This amount can be reduced if the food consumed already contains a lot of water (Priyambodo, 2007).

In pharmacological testing in experimental animals to produce a state of diabetes mellitus can be injected by pancreactomy and chemical substances. Chemicals as diabetogen agents given parental are alloxan and streptozotozin. Aloksan is a diabetagonic that is usually used because this compound quickly causes permanent hyperglycemia within two or three days (Ainia, 2017).

Alloxan is a simple pyrimidine derivative. The alloxan chemical formula is $C_4H_2N_2O_4$ which dissolves freely in water. Aloksan or by another name Mesoxalycarbamida is a condensation compound derived from one molecule of urea with one molecule of mesooksalat acid (Lenzen, 2008, Katiyar, *et al*., 2011) that, administration of alloxan in rats at a dosage of 150 mg / kg bw through an intaperitonial route for 4 days. This diabetagonic compound can cause diabetes mellitus with characteristics similar to type I diabetes mellitus in humans. Alloxan is selectively toxic to pancreatic beta cells (Risdiana, 2016).

Alloxan has two different influences, the first effect of which is alloxan which can inhibit glucokinase production. Glukokinase is a glucose sensor from pancreatic beta cells, so that if glucokinase is inhibited, the specific secretion of insulin will also be inhibited. The second effect, alloxan is able to inject the formation of Reactive Oxygen Species (ROS) which can produce necrosis from pancreatic beta cells. Both of these influences are specific chemical properties of alloxan (Lenzen, 2008).

Alloxan works selectively in the beta cells of the pancreas that are responsible for producing insulin. Alloxan binds to GLUT-2 (glucose carrier) which helps the entry of alloxan into the pancreatic beta cell cytoplasm. Polarized in excess pancreatic beta cells in the mitochondria as a result of the entry of Ca + ions followed by excessive use of energy, causing a lack of energy in the cell. This causes in damage to the number of cells and the period of the pancreatic cells resulting in a decrease in the release of insulin which causes in hyperglycemia (Ainia, 2017).

2.4. Theoretical Framework

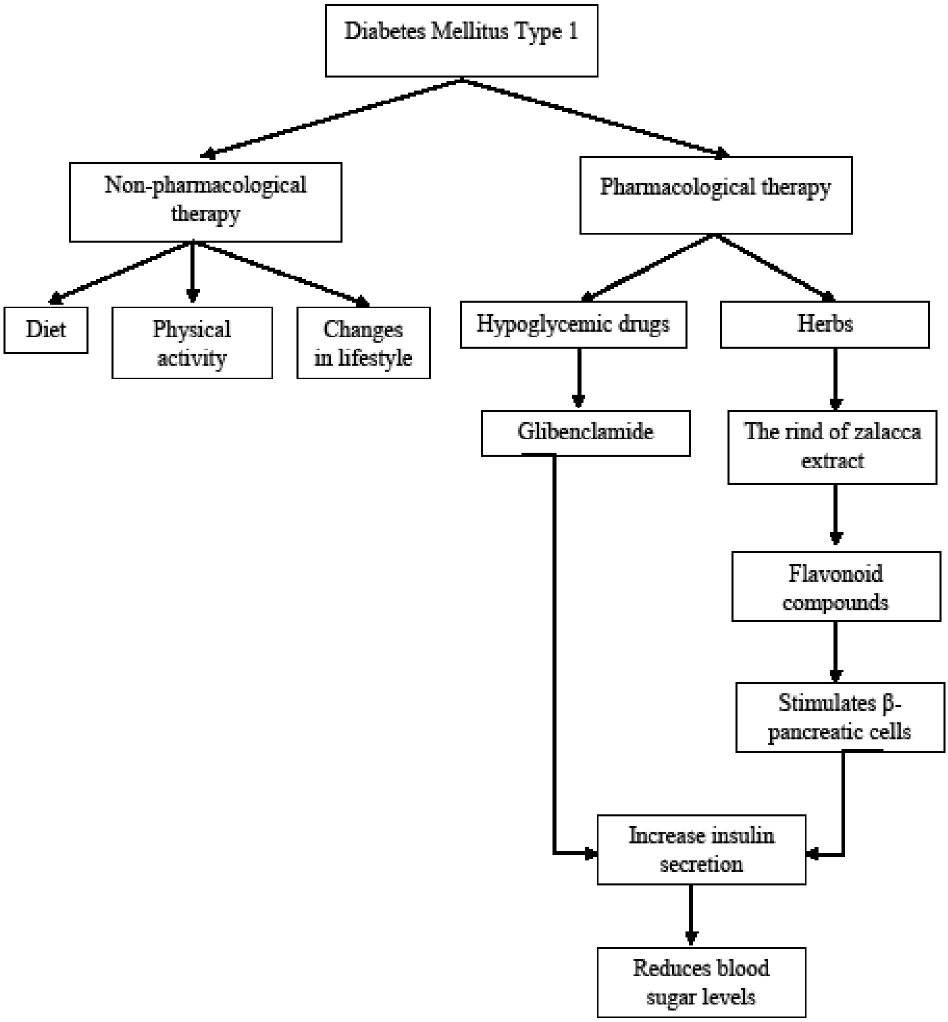


Figure 3. Theoretical Framework

Modified from : Suarsana (2009), Anjani et al. (2015)

2.5. Conceptual Framework

Based on the theoretical framework that diabetes mellitus probably can be overcome by the zalacca rind extract because it can be the effect of blood sugar level.

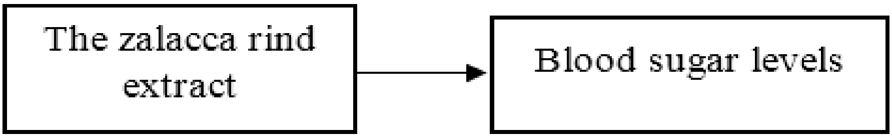


Figure 4. Conseptual Framework

2.6. Hypothesis

Ha : Zalacca (Salacca zalacca [Gaertner] Voss) rind extract can reduce blood sugar level of diabetic white wistar rats (Rattus norvegicus L.)

CHAPTER 3

RESEARCH METHODS

3.1. Research Design

The type of research conducted was true experimental research, with the design of pre post test control group design. The study used 2 groups: the control group and the case group. The control group consisted of positive controls and negative controls. The case group was given a certain dosage zalacca rind extract intervention. The research design can be seen as follows

Pretest		Intervention		Posttest
O1	→	X1	→	O2
O3	→	X2	→	O4
O5	→	X3	→	O6
K1	→	X4	→	K2
K3	→	X5	→	K4

Source: Sugiyono (2012)

Information:

O1, O3, O5 K1, K3	:	Wistar rats with injection of alloxan before intervension
X1	:	Intervention treatment with zalacca rind extract 0.075g/200gW
O2	:	Wistar rats after intervention of zalacca rind extract 0.075g/200gW

X2	:	Intervention treatment with zalacca rind extract 0.15g/200gW
O4	:	Wistar rats after intervention of zalacca rind extract 0.15g/200gW
X3	:	Intervention treatment with zalacca rind extract 0.225g/200gW
O6	:	Wistar rats after intervention of zalacca rind extract 0.225g/200gW
X4	:	Wistar rats without intervention treatment
K2	:	Wistar rats without intervention treatment
X5	:	Intervention treatment with glibenclamid drugs
K4	:	Wistar rats after intervention of glibenclamid drugs

3.2. Location and Time of Research

The research was conducted at the Laboratory of Pharmacy University of Darussalam Gontor and University of Muhammadiyah Yogyakarta for 3 months from January 2019 to March 2019.

3.3. Population and Samples of Research

The research samples were wistar rats (*Rattus norvegicus L*) male wistar weighing 150 - 200 grams with inclusion criteria was no defect healthy, and agile obtained from procurement of experimental animal of Muhammadiyah University of Yogayakarta. The sample used in this research was obtained with calculations by Federer's formula (Federer, 1977)

$$(k - 1)(n - 1) \leq 15$$

$$(5 - 1)(n - 1) \leq 15$$

$$(n - 1) \leq 3{,}75$$

$$(n) \leq 4{,}75 \approx 5$$

Information:

k = Total of Group

n = Number of samples in each group

The experimental animals were divided into 5 treatment groups with samples used in this research were 30 animals with 5 rats in each group. Addition 10% of rats in each group (1 rat) aimed to avoid dropping out.

$N = \frac{n}{1-f}$

N = amount of correction sample

n = amount of the first sample (in the group)

f = estimation of drop out proportion is 10%

$N = \frac{n}{1-f}$

$N = \frac{5}{1-10\%}$

$N = \frac{5}{1-0.1}$

$N = \frac{5}{0.9}$

$N = 5.55 \approx 6$ rats

3.3.1. Sample Inclusion Criteria

1. Male white rat wistar strain
2. Diabetic rat with high blood sugar levels
3. Healthy, active, can adapt

3.3.2. Sample exclusion criteria

1. Rats with healthy conditions
2. Rats with drastic weight lose
3. Previously used in research

3.4. Research Variables

1. Independent variable : Differentiation of the zalacca rind ekstrak
2. Dependent variable: Blood sugar levels

3.5. Operational Definition of Research

Table 2. Operational Definition of Research

Variable	Definition	Methods	Scale
The zalacca rind extract	Types of *pondoh* zalacca obtained from Banjarnegara	Maseration, extracted used vacuum evaporation	Rasio
Blood sugar levels	Measuring blood sugar levels, random plasma glucose test ≥ 200 mg/dl (PERKENI, 2015)	POCT (Point of Care Testing) used glucometer	Interval
Rats	Male white wistar rats (ʻL.), 2-3 months old, with a weight of 150-200 grams	Random	Rasio

3.6. Tools and Materials

1. Tools need:
   a. Rat cage
   b. Animal scales to weigh weight rats
   c. Blood glucose test strip
   d. Glucometer
   e. Rat oral gavage
2. Material:
   a. The zalacca rind
   b. Aquadest as a negative control
   c. Standard food of white rats
   d. Alloxan as an injection of diabetes

3.7. Research Flow

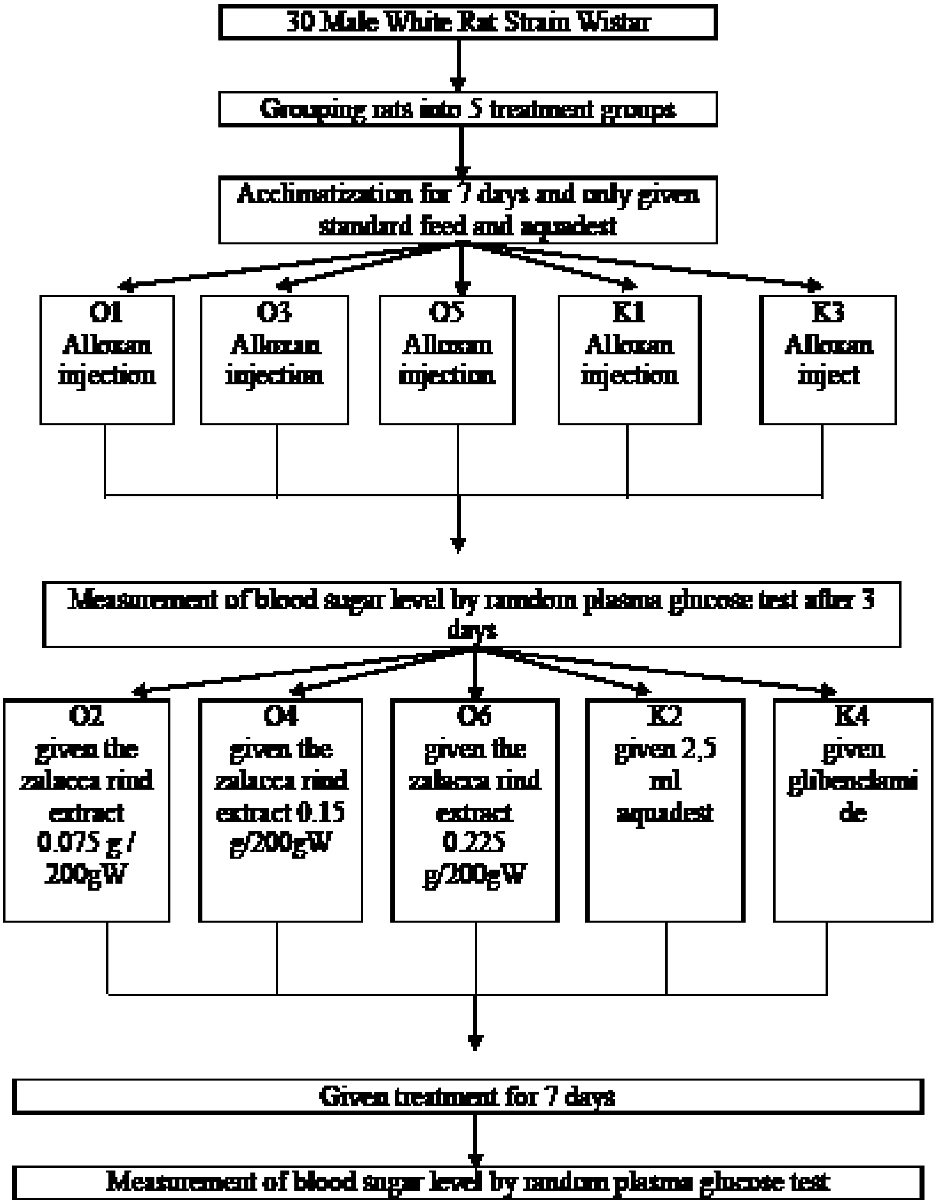


Figure 5. Research Flow

3.8. Research Procedure

Placing experimental animals in the laboratory in accordance with their environment is an important thing that must be considered to optimize the welfare of animals by paying attention to their cages. There are five rats in one cage and made of plastic. Rats were fed standard AD-2 feed and provided drinking water in bottles with pipes with round bullet valves located at the end of the pipe without having to be restricted.

For making the zallaca rind extract, the rind was bought from Banjarnegara with *pondoh* zalacca. Firstly, chop the zalacca rind and dried in the sun to reduce water content. Then mashed using a blender. Weighed for 150 g then extracted using 70% ethanol as much as 900 ml by maceration for 5 days and everyday it must be stirred. Then the extract is filtered using filter paper (filtrate 1). Next, for remaceration using 70% ethanol as much as 600 ml for 2 days and stirred everyday. Then the extract was filtered using filter paper (filtrate 2). Furthermore, filtrate 1 and 2 were combined and evaporated using a vacuum evaporator at temperature of 60°C to separate between extract and ethanol and became to 160 ml. After that, the extract placed in the water bath to evaporate the extract at 60°C until the volume of extract become half, 86 ml until no more ethanol contained in the extract. The extract was stored at 0°C until 15°C. The intervention of the zalacca rind extract using rat oral gavage.

The dosage of the zalacca rind used by adult humans (50 kg) is 100 g with conversion factor dosage from humans (70 kg) to rat (200 g) is 0.018, then the dosage is

$$\frac{70}{50} \text{ x } 100 \text{ x } 0{,}018 = 12.6 \text{ g/kgW}$$ (Kanon *et al*., 2012).

0.15 g the zalacca rind extract equivalent by a dosage the zalacca rind 12.6 g/kgW

Comparison of dosage the zalacca rind extract is:

P1 = 0.075 g/200gW

P2 = 0.15 g/200gW

P3 = 0.225 g/200gW

The dosage of glibenclamide by adult humans is 5 mg, then the dosage of glibenklamid for rats is 5 x 0.018 = 0.45 mg / kgW and added suspension CMC 0.5% weight per volume and then stirred until homogeny sufficient to 5 ml. The intervention of glibenclamid using rat oral gavage (Skolastika, 2009).

The dosage of alloxan was 175 mg/kgW by intraperitoneal. NaCl 0.9% weight per volume used as solvent, just once for injection alloxan and after 3 days measured of blood sugar level (Purnamasari *et al*., 2014, Muhtadi *et al*., 2012, Susilawati *et al*., 2016)

The maximum fluid volume that can be given orally in white rats is 5 ml / 100 gW on negative control. Determination of the maximum dosage used is not recommended to use more than half the maximum fluid volume given. The liquid provided is:

Maximum fluid volume with weight 100 g = 5 ml

Half of the maximum dosage = 2.5 ml

Blood sugar measurements were carried out on the third day after alloxan injection using glucometer. Blood was taken through surface of tail on the perpendicular tract. Taking blood through lateral vein or ventral artery of the tail can be easly done (Peternakan Litbang Pertanian, 2017). The rat's blood sugar was measured two times, first time after alloxan injection and the second time after a week of treatment with the zalacca rind extract. The tools that used was glucometer.

Euthanasia is an end to animal life at the end of research, must be in a human way (Peternakan Litbang Pertanian, 2017). Rats will be euthanized with the aim that the rats that have been used for research are not reused for further research. Type of euthanasia is physically euthanasia by decapitation (beheading of the neck). Before decapitation, first rats were given chloroform with the aim of unconsciousness and easier in the decapitation process, then rats were decapitated with the aim of disappearing immediately reflex blinking and flat electroencephalogram and rats would not feel pain (Isbagio, 1992).

3.9. Data Analysis

Data normality was tested using Shapiro-Wilk. Different test for before and continued by Kruskall-Wallis if the data not distributed normally post hoc by Mann Whitney for analyze different among group were assisted with computer applications.

3.10. Research Ethics

This research has been submitted to Ethical Clearance from Health Research Ethics Committee, Faculty of Medicine University of Muhammadiyah Surakarta. The ethical clearance letter with number 1793/A.1/KEPK-FKUMS/I/2019. 3R principle in using animals in research:

1. Replacement is use of animal with alternative techniques or avoid the use of animal altogether.
2. Reduction is the number of animals used to a minimum to obtain information from fewer animals or more information from the same number of animals.
3. Refinement is the way experiments are carried out, to make sure animals suffer as little as possible (Yurista *et al.,* 2016).

CHAPTER 4

RESULT AND DISCUSSION

3.1. Research Design

The research began from January 20th 2019 to March 28th 2019. The research was conducted at the Laboratory of Pharmacy University of Darussalam Gontor and Muhammadiyah University of Yogyakarta. Making extract for the zalacca rind at the Laboratory of Pharmacy University of Darussalam Gontor and Laboratory of Nutrition. During the research at Muhammadiyah University of Yogyakarta, researcher had been assisted by technicians who helped to provide a rat oral gavage and took care of rat every day.

3.2. Result of Research

The effectiveness test of zalacca rind extract in alloxan injected white rats was carried out once and measured blood sugar levels on the third day. Rats called already diabetic when blood sugar levels over 200 mg / dl and immediately treated. The following are the results of observing blood sugar levels in white rats.

Table 3 showed difference between blood sugar level before and after treatment. The statistical test began with Shapiro-Wilk normality test ($p>0,05$) because the sample of less than 50 samples and the result of statistical test was $p<0.05$ it concluded that the data was not normally distributed then continued by Kruskal-Wallis test. Based on statistic test by Kruskal-Wallis there was no significant difference between groups. Overall, seen from before and after treatment had reduce the blood sugar level caused content of zalacca rind extract but not statistically significant. Glibenclamid is stimulates the secretion of the hormone insulin from pancreatic β cells. Negative control showed that blood sugar level continue to reduce even if not given anything and only normal feed.

Table 3 Blood Sugar Level Before and After Treatment

Group	Blood Sugar Level			Sig
	Before	After	Δ	
Extract 0.075	341.40 ± 146.941	109.80 ± 48.127	231.60 ± 98.895	
Min-Max (mg/dL)	243 - 600	74 -194		
Extract 0.15	373.40 ± 115.032	110.40 ± 40.327	263.00 ± 89.919	
Min-Max (mg/dL)	272 - 539	51 -147		
Extract 0.225	397.80 ± 185.209	122.20 ± 30.858	275.60 ± 194.553	0.559
Min-Max (mg/dL)	241 - 600	98 - 175		
Negative Control	378.00 ±127.442	188.40 ± 24.152	161.20 ± 78.436	
Min-Max (mg/dL)	254 - 536	154 - 342		
Positive Control	313.20 ± 102.758	90.00 ± 21.059	223.20 ± 84.721	
Min-Max (mg/dL)	252 - 493	74 - 125		

Table 4 Relationship Between Group

Group	Related Group	Sig.	Mean
Extract 0.075	Extract 0.15	0.841	Not significantly different
	Extract 0.225	0.222	Not significantly different
	Negative Control	0.032	Significantly different
	Positive Control	0.548	Not significantly different
Extract 0.15	Extract 0.225	0.841	Not significantly different
	Negative Control	0.008	Significantly different
	Positive Control	0.421	Not significantly different
Extract 0.225	Negative Control	0.032	Significantly different
	Positive Control	0.095	Not significantly different
Negative Control	Positive Control	0.008	Significantly different

Among groups, it was found that the results of group extract 0.075 to negative control, 0.15 to negative control, 0.225 to negative control, positive control to negative control were significantly different. Seen from the results of the table above that there were significant differences in the groups extract 0.075, 0.15, 0.225 and positive control if it was related with the negative control.

Dosage of zalacca rind extract converted of rat to zalacca rind of human is $\frac{0.15}{12.6} = \frac{0.075}{b^2}$

$0.15 \times b^2 = 0.075 \times 12.6$

$0.15 \times b^2 = 0.945$

$b^2 = 0.945/0.15$

$\frac{0.15}{12.6} = \frac{0.225}{b^2}$ kgW

$0.15 \times b^2 = 0.225 \times 12.6$

$0.15 \times b^2 = 2.835$

$b^2 = 2.835/0.15$

$= 18.9$ g/kgW

So the dosage of zallaca rind extract converted of rat to zalacca rind of human is 0.075 g/200gW to 6.3g/kgW, 0.15 g/200gW to 12.6 g/kgW and 0.225 g/200gW to 18.9g/kgW.

4.3. Discussion

Alloxan is a diabetogenic substance that causes diabetes because of the mechanism of destruction of β-pancreatic cells as insulin producers. β-pancreatic cells are damaged so insulin has a deficiency and eventually blood glucose increases (Lenzen, 2008). Destruction of beta cells will be followed by a decline in the secretion of the hormone insulin. Insulin deficiency will caused hyperglycemic conditions (Andrianty & Widyaningsih, 2014).

According to Dor (2005), reduce of blood sugar level is caused by regeneration of pancreatic β cells that can still secrete insulin due to the induction of alloxan which does not damage the entire pancreatic β cells. And according to Endang *et al.* (2007), stress condition from the environment will cause motion to become active during blood collection so that the use of tissue glucose increases, this condition decrease blood glucose levels in the body. But this decrease in blood glucose levels is still in a state of diabetic because alloxan causes diabetogenic effect suddenly and selectively damages pancreatic β cells so that it prevents or reduce insulin production.

Difference from previous research of Kanon *et al.* (2012), between this research and previous research used sucrose for induction and this research use alloxan for injection. Sucrose was caused hyperglicemic and not necessarily became diabetic and alloxan caused damage pancreas so that became diabetic. And interview result from Harto Widodo as compiler of book “Olahan Sehat Berkhasiat Obat” stated that type of zalacca that better to use for reduce blood sugar level is local zalacca which tastes rather sweet and smooth but it is difficult to obtain nowadays (because now there are many superior of zalacca planted which are more concerned with sweetness so local zalacca is rarely found in the market).

The research showed that the zalacca rind extract has an effect in decreasing blood sugar levels. The zalacca rind contains flavonoids which have an important role in reducing blood sugar levels by stimulating β-pancreatic cells to produce more insulin (Suarsana, 2009).

Flavonoids have antioxidant activities that can protect the body against damage caused by reactive oxygen so that it can inhibit diseases such as diabetic (Marianne *et al.*, 2011). Flavonoids are able to regenerate damaged β-pancreatic cells so that insulin deficiency can be overcome and play a significant role in increasing the antioxidant enzyme activity (Abdelmoaty *et al*., 2010). Antioxidants can bind radicals so they can reduce insulin resistance (Ruhe & McDonald, 2001). The flavonoids contained in bark extracts have the potential effect to reduce blood sugar levels in alloxan-induced mice, although the statistical results stated that they were not significant.

The zalacca rind contains sinamic acid derivatives which encourage the regeneration of epithelial cells for the repair of pancreatic cells in type 1 diabetes mellitus type 1, arginine which stimulates cell division and strengthens protein synthesis and pterostilben which plays a direct role in reducing blood sugar levels (Widyaningrum *et al.*, 2011). The mechanism of repair of pancreatic cells causes insulin secretion to be better and it returns insulin function in blood sugar metabolism then blood sugar levels decrease even though they do not reach normal conditions because there is a possibility that there is still part of the pancreatic tissue damaged by alloxan (Fitrianingsih, 2015).

Flavonoid compounds can inhibit the activity of α-glucosidase. The α-glucosidase is an enzyme involved in the polysaccharide catabolism process is glycogen degradation. After the α-glucosidase works, a further reaction from the degradation of glycogen by a new phosphorylase can occur. If the α-glucosidase can be inhibited, the catabolism of the polysaccharide can also be inhibited. α-glucosidase activity can prevent blood sugar from rising from the polysaccharide abuse which shows the potential for antidiabetic (Sahputra, 2008).

According to Rohaeti *et al*., (2017) the active ingredient of zalacca rind which is can reduce blood sugar levels are ferulic acid and proline to encourage the formation of collagen and elastin, cinnamic acid derivates which increases cell regeneration, arginine which stimulates cell division and increases protein biosynthesis, pterostilbene can reduce blood sugar levels.

The diabetic is very identical to the pattern of daily life. According to Sheikh of Imam Ibn Baaz said The Prophet Muhammad sallallaahu ‘alaihi wassalam has taught his people to lead healthy lives such as eating before being hungry and stopping before they are full. At the time of the Prophet Muhammad sallallaahu ‘alaihi wassalam there was a physician who was sent from Egypt to Medina, a few months later this physician returned to Egypt because during his duty none of the people were sick and came to get treatment for him, before returning to Egypt this physician asked to Muhammad sallallaahu ‘alaihi wassalam was aware of the secrets that made his people always look healthy and never got sick then he replied,

عن بعض الوفود وفي سنده ضعف ، يروى أنهم قالوا عن النبي صلى الله عليه وسلم (نحن قوم لا نأكل حتى نجوع و إذا أكلنا لا نشبع) يعنون أنهم مقتصدون

“We are a people who do not eat until we become hungry”.

This is corroborated by the opinion of Ayesha as his wife, “In the past Muhammad sallallaahu ‘alaihi wassalam never filled his stomach with (reaching) two types of food. When he was full of bread, he would not eat dates, and when he was full of dates, he would not eat bread. Allah Subhanahu wa Ta’ala said in the Al-Qur’an Surah Al-A’raf (7) 31:

وَكُلُوْا وَاشْرَبُوْا وَلَا تُسْرِفُوْا إِنَّهُ لَا يُحِبُّ الْمُسْرِفِيْنَ

"And eat and drink, but be not excessive. Indeed, He likes not those who commit excess."

CHAPTER 5

CONCLUSION AND SUGGESTION

5.1. Conclusion

1. Effectiveness of zalacca rind extract at a dosage of 0.075 g / 200 gW can reduce blood sugar level but not statistically significant.
2. Effectiveness of zalacca rind extract at a dosage of 0.15 g / 200 gW can reduce blood sugar level but not statistically significant.
3. Effectiveness of zalacca rind extract at a dosage of 0.225 g / 200 gW can reduce blood sugar level but not statistically significant.

5.2. Suggestion

1. For next research expected for extend treatment time for get significant results.
2. For next research expected to examine the safety of zalacca rind extract or side effects from it.

REFERENCES

Abdelmoaty M A, Ibrahim M A, Ahmed N S, and Abdelaziz M A. 2010. Confirmatory Studies on the Antioxidant and Antidiabetic Effect of Quercetin in Rats. *Indian Journal of Clinical Biochemistry*. 25(2) pp.188-192

Agustina K K. 2015. *Kesejahteraan Hewan "Animal Welfare"*. Fakultas Kedokteran. Universitas. Diktat Kuliah.

Ainia N. 2017. *Uji Fitokimia Infusa Pekat Buah Pare (Momodicarcharantia L.) Dan Pengaruh Lama Terapi Dengan Variasi Dosis Terhadap Penurunan Kadar Glukosa Darah Tikus (Rattus Norvegicus) Yang Diinduksi Aloksan*. Skripsi. Fakultas Sain Dan Teknologi. Universitas Islam Malik Ibrahim Malang : Malang

Almatsier S. 2004. *Penuntun Diet*. Jakarta: Gramedia Pustaka Utama.

Al-Qur'an Al-Karim. Surah As-Syu'ara (42) verse 7-8, Surah Al-A'raf (7) 31.

Andrianty S and Widyaningsih T D. 2014. Pengaruh Teh Herbal Berbasis Kulit Salak (Sallaca edulis) Terhadap Kadar Glukosa Darah Dan Profil Lipid Tikus Wistar Jantan Diabetes Melitus Yang Diinduksi Aloksan. *Prosiding Seminar dan Lokakarya Nasional FKPT-TPI*. Malang.

Anjani P P, Andrianty S, and Widyaningsih T D. 2015. Pengaruh Penambahan Pandan Wangi Dan Kayu Manis Pada Teh Herbal Kulit Salak Bagi Penderita Diabetes. *Jurnal Pangan dan Agroindustri.* Vol. 3 No 1 : 203-214.

Apriyanti M. 2012. *Meracik Sendiri Obat & Menu Sehat Bagi Penderita Diabetes Militus*. Yogyakarta : Penerbit Pustaka Baru Press.

Ashari S. 2013. *Salak: The Snake Fruit*. Malang: Tim UB Press.

Baaz, Sheikh Imam Ibn. 2010. Development Group Zad Foundation Sheikh Abdul Aziz bin Baz Charity.

Corwin E J. 2008. *Handbook Of Pathophysiology, 3rd Ed*. USA : Lippincott

Williams & Wilkins, a Wolters Kluwer Business.

Dipiro J T, Talbert R L, Yee G C, Matzke G R, Wells B G, and Posey L M. 2015. Pharmacotherapy : A Patophysiologic Approach, 7th Edition. New York : Mc Graw Hill.

Dor. 2005. Adult Pancreatic β are Performed by Cell Duplication Rather than Stem Cell Differentiation. *Nature, 429*.

Elsner M, Guldbakke B, Tiedge M, Munday R, and Lenzen S. 2000. Relative Importance of Transport and Alkylation for Pancreatic Beta-Cell Toxicity of Streptozotocin. *Diabetologia*.Vol 43 : 1528-1533.

Endang A L. 2007. *Gizi dan Kesehatan Masyarakat. Departemen Gizi dan Indonesia*. Jakarta : PT. Raja Grafindo Persada.

Evacuasiany E, Djojosoewarno P, and Putra I P G D E. 2014. *Pengaruh Ekstrak Kulit Salak (Salacca Zalacca) Terhadap Kadar Gula Darah Pada Mencit Swiss Webster (Mus Musculus) Jantan Dengan Tes Toleransi Glukosa Oral (TTGO)*. Bandung : Bagian Ilmu Farmakologi, Fakultas Kedokteran Universitas Kristen Marantha.

Evert A B and Riddel M C. 2014. *Nutrition Therapy Recomendations for the Management of Adults With Diabetes*. Diabetes Care. Vol 37.

Federer W T. 1977. *Experimental Design Theory And Application, Third Edition*. New Delhi : Oxford and IBH Publishing Co.

Fitrianingsih S P, Lestari F, and Aminah S. 2015. Aktivitas Antihiperglikemia Ekstrak Etanol Kulit Buah Salak (Salacca zalacca (Gaertner) Voss) Terhadap Mencit Diabetes yang Diinduksi Aloksan. *Jurnal Matematika & Sains*. Vol 20 No 1.

Haryoto and Priyatno E. 2018. *Potensi Buah Salak: Sebagai Suplemen Obat dan Pangan*. Surakarta: Muhammadiyah University Press.

Isbagio D W. 1992. Euthanasia pada Hewan Percobaan. *Media Litbangkes*. Vol 2(1), 18-24.

Isdamayani L and Panunggal B. 2015.*Kandungan Flavonoid, Total Fenol, dan Antioksidan Snack Bar Sorgum Sebagai Alternatif Makanan*

Selingan Penderita Diabetes Mellitus Tipe 2. Program Studi Ilm Gizi, Fakultas Kedokteran. Universitas Diponegoro.

Kanon M Q, Fatimawali, and Widdhi B. 2012. Uji Efektivitas Ekstrak Kulit Buah Salak (Salacca zalacca (Gaertn.) Voss) Terhadap Penurunan Kadar Gula Darah Tikus Putih Jantan Galur Wistar (Rattus norvegicus L.) yang Diinduksi Sukrosa. *Jurnal farmasi*. 1(1) : 52-57.

Katiyar D M, Singh B, Lall A M and Haldar C. 2011. Evaluation of Antidiabetic and Hypolipidemic Activity of Chitooligosaccharides in Alloxan Induced Diabetes Mellitus in Mice. *Int. J. of Pharm and Bio Sci*. Vol. 2 (1): 407-416

Kementerian Kesehatan RI. 2007. *Hasil Utama RISKESDAS 2007*. Jakarta : Badan Litbangkes, Depkes RI.

______________________. 2013. *Hasil Utama RISKESDAS 2013*. Jakarta : Badan Litbangkes, Depkes RI.

______________________. 2014. *Situasi dan Analisis Diabetes*. Pusat Data dan Informasi Kementerian Kesehatan RI.

______________________. 2018. *Hasil Utama RISKESDAS 2018*. Jakarta : Badan Litbangkes, Depkes RI.

Krinke G J. 2000. The Handbook of Experimental Animals The Laboratory Rat. New York : Academy Press. Pp. 45-50, 295-296.

Lenzen S. 2008. 2008. The Mechanisms of Alloxan and Streptozotocin Induced Diabetes. Diabetolgia.

Marianne, Yuandani and Rosnani. 2011. Antidiabetic Activity From Ethanol Extract Of Kluwih's Leaf (Artocarpus camansi). *Jurnal Natural*. Vol 11(2) pp.64 - 68.

Muhtadi, Setyowati E, and Azizah T. 2012. Aktifitas Antidiabetes Melitus Ekstrak Kulit Buah Jeruk Manis (Citrus sinensis) dan Kulit Buah Kelengkeng (Euphoria longan (Lour.) Steud) Terhadap Tikus Putih Jantan Galur Wistar yang Diinduksi Aloksan. *Jurnal Penelitian Sains & Teknologi*. Fakultas Farmasi. Universitas Muhammadiyah

Surakarta. Vol. 13, No. 1 : 21-30.

PERKENI. 2015. *Konsensus Pengelolaan Diabetes Mellitus Tipe 2 Di Indonesia 2015*. PB. PERKENI.

Peternakan Litbang Pertanian. 2017. *Penggunaan dan Penanganan Hewan Coba Rodensia dalam Penelitian*. Juknis (Petunjuk Teknis) Rodensia.

Priyambodo S. 2007. *Pengendalian Hama Tikus Terpadu*. Jakarta : Penebar Swadaya.

Profil Kesehatan Indonesia. 2016. *Pusat Data dan Informasi*. Jakarta : Kementerian Kesehatan Republik Indonesia, 2017.

Purnamasari E, Yerizel E, and Efrida. 2014. Pengaruh Pemberian Aspartam Terhadap Kadar Glukosa Darah Tikus Diabetes Melitus Diinduksi Aloksan. *Jurnal Kesehatan Andalas*. Vol 3(3).

Rakieten N, Rakieten M L, and Nadkarni MV. 1963. Studies on The Diabetogenic Action of Streptozotocin (NSC-37917). *Cancer Chemother* Rep. Vol 29:91-98.

Rohaeti E, Fauzi M R, and Batubara I. 2017. Inhibition of α-Glucosidase, Total Phenolic Contetnt and Flavonoid Content on Skin Fruit and Flesh Extract Some Varietes of Snake Fruits. *IOP Publishing* : 58.

Ruhe R C and McDonald R B. 2001. Use of antioxidant nutrient in the prevention and treatment of type 2 diabetes. *J. Am. Coll. Nutr.* 20(5) pp.363-369.

Sahputra F M. 2008. *Potensi Ekstrak Kulit dan Daging Buah Salak Sebagai Antidiabetes*. Skripsi. Bogor : Program Studi Biokimia Fakultas MIPA.

Schnedl W J, Ferber S, Johnson J H, and Newgard C B. 1994. STZ Transport and Cytotoxocity. Specific Enhancement in GLUT2-expressing cells. *Diabetes.* Vol 43 : 1326-1333.

Segal J, Robinson L, and Smith M. 2018. *The Diabetes Diet: Healthy Eating Tips to Prevent, Control, and Reverse Diabetes*. Santa Monica: HelpGuide.

Skolastika M. 2008. *Pengaruh Ekstrak Daun Salam (Syzygyum polyanthum (Wight) Walp) Terhadap Kadar Glukosa Darah Puasa pada Mencit Galur DDY yang Diinduksi Aloksan*. Undergraduate thesis. Fakultas Kedokteran Universitas Kristen Maranatha.

Smith J B and Mangkoewidjojo. 1998. *Pemeliharaan, Pembiakan dan Penggunaan Hewan Percobaan di Daerah Tropis*. Jakarta : UI Press.

Steenis C G G J V. 1975. *Flora Untuk Sekolah di Indonesia.* Jakarta: PT. Pradnya Paramita.

Suarsana I N. 2009. *Aktifitas Hipoglikemik Dan Anti Oksidatif Ekstrak Metanol Tempe Pada Tikus Diabetes*. Thesis. Sekolah Pascasarjana Institut Pertanian Bogor, Bogor.

Sugiyono. 2012. *Metode Penelitian Kuantitatif Kualitatif dan R&D*. Bandung : Penerbit Alfabeta.

Susilawati M D and Muljati S. 2016. Hubungan Antara Intoleransi Glukosa dan Diabetes Melitus dengan Riwayat Tuberkulosis Paru Dewasa di Indonesia (Analisis Lanjut Riskesdas 2013). *Media Litbangkes*, Vol. 26 No. 2: 71-76.

Susilawati Y, Muhtadi A, Moektiwardoyo M, and Arifin P C. 2016. Aktivitas Antidiabetes Ekstrak Daun Iler (Plectranthus scutellarioides (L.) R.Br. Pada Tikus Putih Galur Wistar Dengan Metode Induksi Aloksan. *Jurnal Farmaka*. Volume 14 No 2.

Suskendriyati H, Wijayati A, Hidayah N, and Cahyuningdari D. 2000. Studies on Morphological and Phylogenetic Relationship of Salak Pondoh Varieties (Salacca zalacca (Gaert.) Voss.) at Sleman Highlands. *Biodiversitas*. Vol 1 No 2 Hal: 59-64.

Tijitrosoepomo G. 1988. *Taksonomi Tumbuhan Spermatophyta*. Yogyakarta: Gadjah Mada University Press.

Wahyuni R, Arsunan A A, and Zulkifli A A. 2013. *Factor Releted to Anciety levels in Patient with Diabetes Melitus Type II Bhayangkara Andi Mappa Oudang Hospital*. Universitas Hasanuddin. Makassar.

Widyaningrum H and Tim Solusi Alternatif. 2011. *Kitab Tanaman Obat Nusantara*. Yogyakarta : Media Persindo.

Widyaningsih T D and Andrianty S. 2014. *Pengaruh Teh Herbal Berbasis Kulit Salak (Sallaca edulis) Terhadap Kadar Glukosa Darah dan Profil Lipid Tikus Wistar Jantan Diabetes Melitus yang Diinduksi Aloksan*. Prosiding Seminar dan Lokakarya Nasional FKPT-TPI. Malang : Universitas Brawijaya.

Wohler F and Liebig J. 1838. Untersuchungen Uber Die Natur der Harnsaure [Investigations on The Nature of Uric Acid]. *Ann Pharm* 26 : 241-340 (article in German).

World Health Organization. 2016. *Global Report On Diabetes*. Geneva : WHO Press.

______________________. 2018. *Diabetes*. http://www.who.int/newsroom/fact-sheets/detail/diabetes. Diakses pada tanggal 2 November 2018.

Wulangi K. 1999. *Prinsip-prinsip Fisiologi Hewan.* Proyek Pembinaan Tenaga Kependidikan Dirjen Dikti. Jakarta.

Appendix 1. Statistic Test

Test of normality before treatment

Tests of Normality

	Kolmogorov-Smirnov[a]			Shapiro-Wilk		
	Statistic	df	Sig.	Statistic	df	Sig.
sebelum	.272	25	.000	.785	25	.000

a. Lilliefors Significance Correction

Test Statistics[a,b]

	sebelum
Chi-Square	1.985
df	4
Asymp. Sig.	.739

a. Kruskal Wallis Test

Test of normality after treatment

Tests of Normality

	Kolmogorov-Smirnov[a]			Shapiro-Wilk		
	Statistic	df	Sig.	Statistic	df	Sig.
sesudah	.171	25	.058	.848	25	.002

a. Lilliefors Significance Correction

Test Statistics[a,b]

	sesudah
Chi-Square	12.127
df	4
Asymp. Sig.	.016

a. Kruskal Wallis Test

b. Grouping Variable: kelompok

Mann-Whitney Test (Group O1-O2)

Test Statistics[b]

	sesudah
Mann-Whitney U	11.000
Wilcoxon W	26.000
Z	-.313
Asymp. Sig. (2-tailed)	.754
Exact Sig. [2*(1-tailed Sig.)]	.841[a]

a. Not corrected for ties.

b. Grouping Variable: kelompok

Mann-Whitney Test (Group O1-O3)

Test Statistics[b]

	sesudah
Mann-Whitney U	6.000
Wilcoxon W	21.000
Z	-1.358
Asymp. Sig. (2-tailed)	.175
Exact Sig. [2*(1-tailed Sig.)]	.222[a]

a. Not corrected for ties.

b. Grouping Variable: kelompok

Mann-Whitney Test (Group O1-K(-))

Test Statistics[b]

	sesudah
Mann-Whitney U	2.000
Wilcoxon W	17.000
Z	-2.193
Asymp. Sig. (2-tailed)	.028
Exact Sig. [2*(1-tailed Sig.)]	.032[a]

a. Not corrected for ties.

b. Grouping Variable: kelompok

Mann-Whitney Test (Group O1-K(+))

Test Statistics[b]

	sesudah
Mann-Whitney U	9.000
Wilcoxon W	24.000
Z	-.736
Asymp. Sig. (2-tailed)	.462
Exact Sig. [2*(1-tailed Sig.)]	.548[a]

a. Not corrected for ties.

b. Grouping Variable: kelompok

Mann-Whitney Test (Group O2-O3)

Test Statistics[b]

	sesudah
Mann-Whitney U	11.000
Wilcoxon W	26.000
Z	-.313
Asymp. Sig. (2-tailed)	.754
Exact Sig. [2*(1-tailed Sig.)]	.841[a]

a. Not corrected for ties.

b. Grouping Variable: kelompok

Mann-Whitney Test (Group O2-K(-))

Test Statistics[b]

	sesudah
Mann-Whitney U	.000
Wilcoxon W	15.000
Z	-2.611
Asymp. Sig. (2-tailed)	.009
Exact Sig. [2*(1-tailed Sig.)]	.008[a]

a. Not corrected for ties.

b. Grouping Variable: kelompok

Mann-Whitney Test (Group O2-K(+))

Test Statistics[b]

	sesudah
Mann-Whitney U	8.000
Wilcoxon W	23.000
Z	-.940
Asymp. Sig. (2-tailed)	.347
Exact Sig. [2*(1-tailed Sig.)]	.421[a]

a. Not corrected for ties.

b. Grouping Variable: kelompok

Mann-Whitney Test (Group O3-K(-))

Test Statistics[b]

	sesudah
Mann-Whitney U	2.000
Wilcoxon W	17.000
Z	-2.193
Asymp. Sig. (2-tailed)	.028
Exact Sig. [2*(1-tailed Sig.)]	.032[a]

a. Not corrected for ties.

b. Grouping Variable: kelompok

Mann-Whitney Test (Group O3-K(+))

Test Statistics[b]

	sesudah
Mann-Whitney U	4.000
Wilcoxon W	19.000
Z	-1.776
Asymp. Sig. (2-tailed)	.076
Exact Sig. [2*(1-tailed Sig.)]	.095[a]

a. Not corrected for ties.

b. Grouping Variable: kelompok

Mann-Whitney Test (Group K(+)-K(-))

Test Statistics[b]

	sesudah
Mann-Whitney U	.000
Wilcoxon W	15.000
Z	-2.611
Asymp. Sig. (2-tailed)	.009
Exact Sig. [2*(1-tailed Sig.)]	.008[a]

a. Not corrected for ties.

b. Grouping Variable: kelompok

Test of normality different of treatment

Tests of Normality

	Kolmogorov-Smirnov[a]			Shapiro-Wilk		
	Statistic	df	Sig.	Statistic	df	Sig.
selisih	.187	25	.025	.896	25	.015

a. Lilliefors Significance Correction

Test Statistics[a,b]

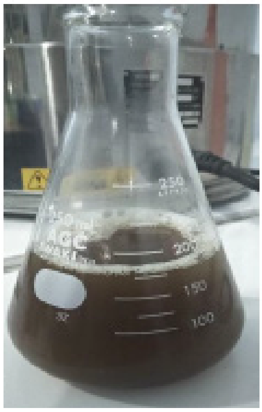
	selisih
Chi-Square	2.995
df	4
Asymp. Sig.	.559

a. Kruskal Wallis Test

b. Grouping Variable: kelompok

Appendix 2. Documentation

Maceration Process



Zalacca rind extract before evaporation process in the water bath

Zalacca rind extract after evaporation process in the water bath

Cage of rats

Glucometer for measure blood sugar level