TEST BLOOD GLUCOSE LEVELS USING ANTIDIABETIC DRUG IN white mice (RATTUS NOVERGICUS)

Nur Afni M Nento1), Nilawaty Nurkamiden2), and Author Tiga3)
[1,2,3)]Bina Mandiri University Gorontalo
Email: nurafninento05@gmail.com

ABSTRACT

The purpose of this research is to find outpharmacological effects caused by antidiabetic drugs on White Rats (Rattus novergicus).In this study, we used white rats for antidiabetic test. This study was conducted, so that we know more about the effectiveness of antidiabetic drugs. In addition, as pharmacy students we must know which antidiabetic drugs are ideal and do not have side effects that are detrimental to users of these drugs. The main parameter of antidiabetic is blood glucose level.

The method used is an experimental method using experimental animals in the form of white rats (Rattus novergicus). This research was conducted at the pharmacy laboratory of Bina Mandiri University, Gorontalo, the method used was an experimental method using experimental animals in the form of white rats (Rattus novergicus), where first white rats were fasted for 8 hours, then the rats' initial blood sugar was measured using a glucometer, after that 2 ml of 50% glucose was given.

The results showed that the effect of antidiabetic drugs used, namely glibenclamide, metformin, glokovance on blood sugar levels in experimental white rats (Rattus novergicus) could provide a therapeutic effect that could lower blood sugar levels.

Keywords:blood glucose, glibenclamide, metformin, and glokovance

PRELIMINARY

Pharmacy is a profession related to health sciences and chemistry, especially about drugs. In pharmacy we learn about pharmacology. Pharmacology is the study of the relationship between drugs and living things.

From this understanding we can conclude that pharmacology has a special relationship with pharmacy, namely how to make, formulate, store and provide drugs. In making medicine, we should also learn about toxicology.

Toxicology is the study of the adverse effects or effects of drug poisoning. Pharmacology and toxicology is the science that deals with the basic principles of drug action.

Drugs are substances used to diagnose, reduce pain, and treat and prevent disease. Apart from medicineIn the human body there are separate settings that can be used to prevent the formation of a disease. And the hormones produced by the body that work as previously mentioned. One of the hormones that have a function in regulating the metabolism and circulation of glucose in the body is the hormone insulin. This hormone is formed in the pancreas gland by the cells that secrete the insulin [2]

The hormone insulin is used to bind glucose in the blood so that there is no accumulation of glucose in the blood and causes the glucose to be excreted in the urine without being used. This can cause the body to become tired, thirsty, hungry

and urinate frequently. This is a symptom of diabetes mellitus [2]

In this study, we used white rats for antidiabetic test. This study was conducted, so that we know more about the effectiveness of antidiabetic drugs. In addition, as pharmacy students we must know which antidiabetic drugs are ideal and do not have side effects that are detrimental to users of these drugs. The main parameter of antidiabetic is blood glucose level [2]

Diabetes mellitus is a condition that arises due to relative or absolute insulin deficiency. Hyperglycemia arises because the absorption of glucose into cells is inhibited and its metabolism is disrupted. Under normal circumstances, about 50% of the glucose consumed is completely metabolized to CO and water, 5% is converted to glycogen and about 30-40% is converted to fat. In Diabetes Mellitus all these processes are disturbed, glucose cannot enter the cells, so energy is mainly obtained from protein and fat metabolism [4]

Diabetes Mellitus is an increase in blood glucose levels or hyperglycemia (fasting glucose 126 mg/dL or postprandial 200 mg/dL or glucose when 200 mg/dL. If DM is not treated immediately there will be disturbances in fat and protein metabolism, and the risk of developing disorders increased microvascular or macrovascular [4]

Diabetes mellitus (DM) is a metabolic disorder characterized by hyperglycemia associated with abnormalities of carbohydrate, fat and protein metabolism caused by decreased insulin secretion or decreased insulin sensitivity. [15]

Diabetes Mellitus or diabetes or diabetes is a disease characterized by blood glucose levels that exceed normal (hyperglycemia) due to the body's lack of insulin, both absolute and relative. The level of blood glucose levels determines whether a person suffers from Diabetes Mellitus or not [5]

The most important metabolic disorders are carbohydrate metabolism disorders. Therefore, the diagnosis of diabetes mellitus is always based on glucose levels in blood plasma [1]

In diabetes mellitus all processes are disrupted, glucose cannot enter the cells, so energy is mainly obtained from protein and fat metabolism. In fact, hyperglycemia itself is relatively harmless, except when it is so severe that the blood becomes hyperosmotic with respect to intracellular fluid. The real danger is the resulting gliosuria, because glucose is an osmotic diuretic, so diuresis is greatly increased with the loss of various electrolyte effects. This causes dehydration and electrolyte loss in untreated diabetics. Due to dehydration, the body tries to overcome it by drinking a lot (polydipsia). The body loses 4 calories for every gram of glucose excreted per day [7]

Insulin is a polypeptide with a molecular weight of approximately 6000. This polypeptide consists of 51 amino acids arranged in two chains, the A chain consists of 21 amino acids and the B chain consists of 30 amino acids. Between chains A and B there are 2 disulfide bridges, namely between A-7 with B-7 and A-20 with B-19. Besides that, there is still a disulfide bridge between the 6th and 11th amino acids in the A chain. Because porcine insulin is more similar to human insulin, it is easy to produce semisynthetic human insulin using porcine insulin. Besides that, human insulin can also be synthesized using recombinant DNA techniques [4]

Insulin secretion is regulated not only by blood glucose levels but also by other hormones and autonomic mediators. Insulin secretion is generally stimulated by uptake of high blood glucose and is phosphorylated in pancreatic cells. Insulin

is generally isolated from the pancreas of cattle and pigs, but human insulin can also replace animal hormones for therapy. Human insulin is produced by a special strain of E. Coli that has been genetically altered. contains the gene for human insulin. Pig insulin is closest in structure to human insulin, being distinguished by only one amino acid. Symptoms of hypoglycemia are the most common and serious side reaction of an overdose of insulin. Other side reactions in the form of lipodystrophy and allergic reactions. Diabetes mellitus is a condition that arises due to relative or absolute insulin deficiency. Hyperglycemia arises because the absorption of glucose into cells is inhibited and its metabolism is disrupted. Under normal circumstances, approximately 50% of the glucose eaten undergoes complete metabolism into CO2 and water, 5% is converted to glycogen and approximately 30-40% is converted to fat [10]

Mechanism of Diabetes:Diabetes mellitus is characterized by high levels of glucose in the blood or hyperglycemia. The initial symptom of diabetes mellitus is usually polyurea as a result of increased diuresis determined by osmosis, the next symptom that arises is glycosuria when the hyperglycemia condition exceeds 180 mg/dL (normal blood sugar level 80-100 mg/dL. Hyperglycaemia occurs later caused by mobilization of fat stores, especially because the increased free fatty acid concentration will cause lethargy and severe acidosis and cause comadiabetic. Hyperglipidemia occurs because the absorption of glucose into cells is inhibited and metabolism is disturbed. Under normal conditions, approximately 50% of glucose enters the body undergo complete metabolism into CO2 and H2O in adipose tissue through the process of glycolysis,

Carbohydrates are digested into glucose so that blood glucose levels increase. Insulin plays a role in maintaining normal blood glucose levels by transferring blood glucose into the cells that make up blood glucose which cannot be used directly into energy through the process of oxidation (respiration).

C6H12O6 + 6CO2 --□ 6CO2 + 6H2O + energy

The most severe form of diabetic disorder is diabetes, there is a disturbance in the biochemical process of blood glucose in the body, namely the occurrence of ketoacidosis due to the formation of large amounts of ketone bodies. Elimination of glucose in the urine causes an osmotic diuresis with water loss, thus diabetic digestion is dependent on acidosis. [2]

According to Istiarini 2009. Diabetes Mellitus is a complex chronic disease that involves abnormalities in metabolism, fat, carbohydrates, protein and the development of macrovascular and neurological complications.

Symptoms of Diabetes Mellitus [13]

a. Poluria (excessive urination)
b. Polydipsia (drink a lot)
c. Polyphagia (a lot of eating)

Symptoms of diabetes mellitus from one patient to another patient are not always the same. The symptoms mentioned below are symptoms that generally occur without reducing the possibility of a variety of other symptoms. There are also people with diabetes mellitus who do not show any symptoms until a certain time [13]

Pregnant women often experience disruption or death of the fetus in the womb, or give birth to babies weighing more than 3.5 kg. [13]

Besides rising blood sugar levels, diabetes is characterized by the presence of sugar in the urine (glycosuria) and a lot of urination because the glucose excreted binds a lot of water. As a result, you feel

very thirsty, lose energy, lose weight and feel tired. The body begins to burn fat to meet its energy needs, which is accompanied by the formation of reforming substances including acetone, hydroxybutyric acid and diacetate, which make the blood acidic. This condition, which is called ketoacidosis and especially occurs in type 1, is very dangerous because it can eventually lead to fainting. The breath of patients who have become very thin often also smells of acetone [9]

The cause is a lack of the hormone insulin, which functions to utilize glucose as an energy source and synthesize fat. As a result, glucose builds up in the blood (hyperglycemia) and is eventually excreted in the urine without being used (glycosuria). Therefore, urinary production is greatly increased and the patient has to urinate, feels very thirsty, loses weight and feels tired [3]

According to Riyadi, S. and Sukarmin, (2011), the classification of Diabetes Mellitus and other classifications of glucose intolerance are:

1. Insulin Dependent Diabetes Mellitus (IDDM) is insulin deficiency due to Langerhans cell cell damage associated with a specific HLA (Human Leucocyte Antigen) type, predisposing to autoimmune phenomenon insulitis. This disorder occurs due to damage to the immune system (immune) which then destroys Langerhans cells in the pancreas. This abnormality results in a decrease in insulin production
2. Non-Insulin Dependent Diabetes Mellitus (NIDDM) is resistant diabetes, more common in adults, but can occur at any age. Most people who are overweight, there is a familiar trend, may need insulin when hyperglycemic during stress.
3. Other types of Diabetes Mellitus Other types of Diabetes Mellitus, namely DM associated with certain conditions or hyperglycemic syndromes occur due to other diseases, pancreatic disease, hormones, drugs or chemicals, endocrinopathy, insulin receptor disorders, certain genetic syndromes.
4. Impaired Glucose Tolerance (impaired glucose tolerance) Glucose levels between normal and diabetes, can become diabetes or become normal or remain unchanged.
5. Gastrointestinal Diabetes Mellitus (GDM) Glucose intolerance that occurs during pregnancy, changes in endocrine and carbohydrate metabolism that support heating food for the fetus and preparation for breastfeeding. Towards term, insulin requirements increase so that it reaches 3 times the normal state. If a mother is not able to increase insulin production so that it is relatively hypoinsulin, it will result in hyperglycemia. Insulin resistance is also caused by the presence of the hormones estrogen, progesterone, prolactin and placental lactogen, these hormones affect insulin receptors on cells, thereby reducing insulin activity.

There are some risk factors for diabetes mellitus that must get serious attention to be able to avoid this disease that can be considered very deadly, namely:

1. Family History

   Hereditary or genetic factors have a contribution that cannot be underestimated for someone developing diabetes. Eliminating genetic factors is very difficult. What can be done for someone to avoid diabetes mellitus because of genetic causes is to improve lifestyle and diet.
2. Obesity Or Overweight

   Obesity can cause a person's body to experience resistance to the hormone insulin. The body's cells compete with adipose tissue to absorb insulin. As a result, the pancreas organ

will be stimulated to produce insulin as much as possible so that this organ becomes tired and eventually damaged.

3. Increasing age

   At the age of 40 years, many vital organs weaken and the body begins to experience sensitivity to insulin. Even women who have experienced menopause have a tendency to be more insensitive to the hormone insulin.

4. Lack of Physical Activity

   Lack of physical activity is a big enough factor for someone to be overweight and weaken the work of vital organs such as the heart, liver, kidneys and pancreas.

5. Smoke

   Cigarette acid turns out to have negative effects on health and its nature is very complex. Including the risk of someone susceptible to diabetes mellitus.

6. Consuming cholesterol foods

   High Cholesterol foods are also believed to make a high enough contribution to someone prone to diabetes mellitus.

7. Stress in the long term

   Severe stress conditions can disrupt the balance of various hormones in the body, including the production of the hormone insulin. Besides, stress can spur the body's cells to be wild which has the potential for a person to be affectedcancer It also triggers the body's cells to become insensitive or resistant to the hormone insulin.

8. Hypertension or high blood

   Keep your blood pressure below 140/90 mmHg. Don't eat too much salty food. Excess salt triggers a person to suffer from high blood pressure which in turn plays a role in increasing the risk of developing diabetes mellitus.

9. Pregnancy

   During pregnancy, the placenta produces hormones that disrupt the balance of the insulin hormone and in certain cases triggers the body's cells to become resistant to the hormone insulin. This condition usually returns to normal after pregnancy or postpartum. However, it becomes very risky for babies who are born to have the potential for diabetes mellitus in the future.

Endocrine comes from the Greek which means "secret into". The blind glands produce secretions not through certain channels but directly into the blood circulation, namely hormones. The endocrine system regulates and maintains body functions and body metabolism, if endocrine disorders occur, it will cause complex problems, especially the metabolism of body functions is disturbed. absolute or relative due to metabolism of carbohydrates, fats and proteins. The endocrine system interacts with the nervous system to regulate and coordinate body activities. Endocrine control is mediated by chemical messengers called hormones, these hormones are released by the endocrine glands into body fluids, absorbed into blood fluids,

Hormones affect target cells through hormone receptors, which are protein molecules that have binding properties for certain hormones. The body's hormonal response is usually slower, of longer duration, and more widely distributed than the direct response of muscles and glands to nervous system stimulation.

Endocrine glands are not waste glands, endocrine glands have a secretory effect which means that they have been secreted to be processed and reused. These secretions produce hormones that will be secreted through the blood circulation and then reach the target cell. This endocrine gland works with a feedback mechanism, which means that

there will be a reciprocal tone from the destination organ in the form of an effect [15]

Types of Glands in the Endocrine System

1. The anterior and posterior pituitary glands

   The pituitary is also known as the pituitary gland. The pituitary is a small gland in the bony cavity located at the base of the brain below the hypothalamus about 2 cm. It is connected to the hypothalamus by a small stalk (infundibulum). The pituitary gland is called the master gland because it can produce hormones and hormones produced by the pituitary can stimulate other glands to produce other hormones [16]

   a. Posterior pituitary gland

      Embryologically, the posterior pituitary gland originates from the growth of the brain consisting of nerve tissue (neurohypophysis). The posterior pituitary is connected to the hypothalamus via neural pathways. The posterior pituitary forms a neurosecretory system that secretes vasopressin and oxytocin. Hormone secretion from the posterior pituitary is controlled by the hypothalamus [12]

   b. anterior pituitary gland

      The anterior pituitary gland consists of glandular epithelial tissue originating from a protrusion of the roof of the mouth called the adenohypophysis. The arterial pituitary is connected via blood vessels. Hormone secretion from the interior is controlled by the hypothalamus [12]

2. Thyroid Gland

   The thyroid gland is one of the largest endocrine glands in the human body. This gland can be found in the neck. This gland functions to regulate the speed at which the body burns energy, makes protein and regulates the body's sensitivity to other hormones [11]

3. Parathyroid glands

   There are two types of parathyroid gland cells, there are main cells that secrete parathyroid hormone (PTH) which functions as a controller of calcium and phosphate balance in the body through increasing blood calcium levels and decreasing blood phosphate levels on an oxyphilic basis which is the development stage of chief cells [11]

4. thymus

   The thymus gland is a gland that is responsible for human growth. The thymus gland is even very influential at the time of growth [1]

5. Adrenaline

   The adrenal glands or adrenal glands are located above the left and right kidneys. The outer part of the adrenal gland is yellowish which produces cortisol called the cortex, the medulla which produces adrenaline and non-adrenaline.

6. Pancreas

   The pancreas gland belongs to the group of endocrine glands. There are several groups of cells in the pancreas known as the islets of Langerhans. This section functions as an endokarin gland that produces the hormone insulin.

7. Gonads

   The sex glands (gonads) are endocrine glands that produce and secrete steroids that regulate body development and control secondary sexual characteristics.

Important Uses of the Endocrine System

Some of the uses of the endocrine system are:

1. Homeostasis (temperature, metabolism, nutrition, acid base balance)
2. Combating stress (infection, trauma, shock)
3. Growth and development (increase the number of cells and increase the size of cells
4. Reproduction (secrete male and female sex hormones).

RESEARCH METHODS

This research was conducted at the pharmacy laboratory of Bina Mandiri University, Gorontalo, the method used was an experimental method using experimental animals in the form of white rats (Rattus novergicus), where first white rats were fasted for 8 hours, then the rats' initial blood sugar was measured using a glucometer, after that 2 ml of 50% glucose was given. White rats were then left for 15 minutes, after which the blood sugar levels of white rats were measured again. After that, Na CMC/ Metformin/ Glukovance/ Glibenclamide were given. Then re-measured the sugar levels of white rats and finally the comparison of initial blood sugar and blood sugar after being given the drug was carried out

Tools and Materials

The tools used for this practicum are glucometer, beaker, hot plate, cannula, mortar and pestle, analytical balance.

The materials used in this practicum are distilled water, 50% glucose, glibenclamide, glokovance, parchment paper, metformin, Na CMC.

Work procedures

1. Prepare tools and materials
2. Prepared experimental animals in the form of mice
3. Rats are fasted for about 8 hours
4. 4 mice were weighed
5. Rats marked
6. Measure the initial blood sugar of mice using a glucometer
7. Give 50% glucose as much as 2 ml
8. Leave it for 15 minutes
9. Measuring blood sugar levels of white rats
10. Given Na CMC as much as 2 mlMC
11. The rat's blood sugar was measured again
12. Record the ratio of the rat's blood sugar
13. Repeat the above procedure by replacing Na CMC with metformin, glokovance and glibenclamide.

RESEARCH RESULT

The first white rat (Rattusnovergicus) was checked for initial blood sugar, which was 96, then 50% glucose was given, the rat's blood sugar rose to 236. Then after being given the drug Na CMC, the rat's blood sugar dropped to 105. So Na CMC has the potential as an antidiabetic drug.

In white rat 2 (Rattusnovergicus) the first blood sugar check was 109, then 50% glucose was given, the rat's blood sugar rose to 196, then after being given Metformin the rat's blood sugar dropped to 102. So Metformin has the potential as an antidiabetic drug.

In white rats 3 (Rattusnovergicus) the first blood sugar check was 183, then 50% glucose was given, the mice's blood sugar rose to 187, then after being given the drug Glukovance the rat's blood sugar dropped to 171. So Glukovance has the potential as an antidiabetic drug.

In white rat 4 (Rattusnovergicus) first, the initial blood sugar check was 81, then 50% glucose was given, the rat's blood sugar rose to 275. Then after being given the drug Glibenclamide, the rat's blood sugar dropped to 185. So Glibenclamide has the potential as an antidiabetic drug.

Table 1. The results of the observation of blood glucose levels in rats

No	Try Animals	Initial Blood Sugar	Blood Sugar + Glucose + Medicine

		Blood Sugar	+ Glucose 50%	glukovance	Gliben Chlamyd	Metformin	Na CMC
1	Rat (Rattus novergicus)	96	236	-	-	-	105
2	Rat (Rattus novergicus)	109	196	-	-	102	-
3	Rat (Rattus novergicus)	183	187	171	-	-	-
4	Rat (Rattus novergicus)	81	275	-	185	-	-

DISCUSSION

Diabetes mellitus, diabetes or diabetes is a chronic disorder in particular the metabolism of carbohydrates in the body, and also of fat and protein metabolism (lat. Diabetes = transmission, mellitus = honey). The reason is a lack of the hormone insulin to use (burn) glucose as an energy source and for fat synthesis, with the effect of hyperglycemia. Diabetes Mellitus or diabetes or diabetes is a disease characterized by blood glucose levels that exceed normal (hyperglycemia) due to the body's lack of insulin, both absolute and relative. The level of blood glucose levels determines whether a person has diabetes mellitus or not [5]

The symptoms of diabetes mellitus are polyuria, which is a large volume of urine or frequent urination, polypsia, which is a lack of fluid in the body, polyphagia, which is a large amount of food that can cause an increase in blood glucose.

This study used a glucometer, with the reason that the glycometer is an automatic tool that makes it easy to obtain blood glucose results, examination using this tool requires a relatively short, accurate time, the test time is at least 30 seconds. The way to use the glucometer is to prepare the glucotest strip and tool, insert the glucotest strip into the tip of the glucometer, put a drop of blood on the glucotest strip reagent, then read the sugar level listed on the glucometer screen, where the working mechanism of the glucometer is in the strip there is a glucooxygenase enzyme which if a blood sample hits the strip it will be directly read by the glucometer

The purpose of this study was to prove the hypoglycemic effect of blood glucose-lowering drugs given to experimental animals (white rats).

The first thing to do is measure the initial glucose level in rat 1 and the results for rat 1 the initial glucose level is 96 mg/dl. Then the experimental animal was injected with 2 ml of glucose, after that the sugar level of rat 1 was measured using a glucometer and the results were that the blood sugar of rat 1 rose to 236 mg/dl, then the experimental animal was allowed to stand for 15 minutes, after 15 minutes the experimental animal was injected 2 ml of Na CMC was then measured again in the blood sugar of rat 1 and the results showed that the sugar level of rat 1 dropped to 105 mg/dl. This states that NaCmc can be efficacious as a blood sugar-lowering drug.

Then for rat 2, the first thing to do is measure the initial glucose level in rat 2 and the results for rat 2 the initial glucose level is 109 mg/dl. Then the experimental animal was injected with 2 ml of glucose after that the sugar level of rat 2 was measured using a glucometer and the results were that the blood sugar of rat 2 rose to 196 mg/dl, then the experimental animal was allowed to stand for 15 minutes, after 15 minutes the experimental animal was injected 2 ml of metformin

was then measured again in the blood sugar of rat 2 and the result was that the sugar level of rat 2 fell to 102 mg/dl. This states that metformin can be efficacious as a blood sugar-lowering drug.

Then for mice 3 the first thing to do is measure the initial glucose levels in mice 3 and the results for mice 3 that the initial glucose level is 183 mg/dl. Then the experimental animal was injected with 2 ml of glucose after that the sugar level of the 3 mice was measured using a glucometer and the results were that the blood sugar of the 3 mice rose to 187 mg/dl, then the experimental animals were allowed to stand for 15 minutes, after 15 minutes the experimental animals were injected 2 ml of glokovance was then measured again in the blood sugar of rat 3 and the result was that the sugar level of rat 3 fell to 171 mg/dl. This states that glukovance can be efficacious as a blood sugar-lowering drug.

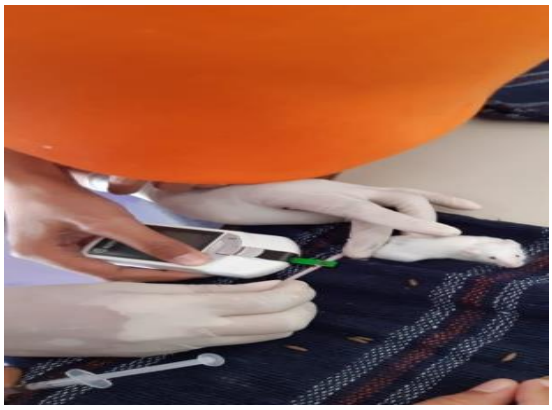

Figure 1. Measurement of blood sugar levels

Then for rats 4 the first thing to do is measure the initial glucose levels in rats 4 and the results for mice 4 that the initial glucose level is 81 mg/dl. Then the experimental animal was injected with 2 ml of glucose after that the sugar level of the 4 mice was measured using a glucometer and the results were that the blood sugar of the 4 mice rose to 275 mg/dl, then the experimental animals were allowed to stand for 15 minutes, after 15 minutes the experimental animals were injected 2 ml of metformin was then re-measured the blood sugar of rat 4 and the result was that the sugar level of rat 4 dropped to 185mg/dl. This states that glibenclamide can be efficacious as a blood sugar-lowering drug.

Figure 2. Drug taking

The results showed that all the drugs used in this endocrine study can be efficacious as drugs to lower blood sugar levels.[7]

CONCLUSION

Diabetes mellitus (DM) is a metabolic disorder characterized by hyperglycemia associated with abnormalities of carbohydrate, fat and protein metabolism caused by decreased insulin secretion or decreased insulin sensitivity. Rising blood sugar levels are characterized by the presence of sugar in the urine (glycosuria) and a lot of urination because the glucose excreted binds a lot of water. As a result, you feel very thirsty, lose energy, lose weight and feel tired. In Diabetes Mellitus, all of these processes are disrupted, glucose cannot enter the cells, so energy is mainly obtained from protein and fat metabolism

The effect of antidiabetic drugs used, namely glibenclamide, metformin glycovance, on blood sugar levels in experimental white rats (Rattus novergicus) can provide a therapeutic effect that can lower blood sugar levels.

As a recommendation in this study, researchers should be more careful in handling experimental animals and do things according to the instructions in winning mice so that there is less risk of being bitten by white rats.

BIBLIOGRAPHY

[1] Adam,JMF 2000. New classification and diagnostic criteria for diabetes mellitus. Mirror of the World of MedicineNo. 127.

[2] Campbell, Neil A. et al. 2004. Biology Fifth Edition Volume 3. Erlangga. Jakarta.

[3] Ministry of Health of the Republic of Indonesia. 2005. Pharmaceutical Care for Diabetes Mellitus. Jakarta: Directorate of Community and Clinical Pharmacy.

[4] Ganiswara, et al. 1995. Pharmacology and Therapy IV edition. Department of Pharmacology and Therapeutics FK UI. Jakarta

[5] Hastuti, RT 2008. Risk Factors for Diabetic Ulcers in Patients with Diabetes Mellitus in Dr. Hospital. Moewardi Surakarta

[6] Istiarini, 2009. Effect of reflexology therapy on blood sugar levels in Type II DM clients in the context of Nursing Care in Sleman

[7] Katzung,G. Bertram. 2002. Pharmacology: Basic and Clinical. Book 2. Jakarta: Salemba Medika Publisher.

[8] Riyadi, S., & Sukarmin, 2011. Nursing Care in Patients with Exocrine and Endocrine Disorders of the pancreas. Yogyakarta: Graha Ilmu

[9] Ukandar, EY,JI Sigit, IK Adnyana, AAP Setiadi, Kusnandar. 2008. ISO Pharmacotherapy. Publisher PT. ISFI Publishing. Jakarta

[10] Soegondo,S. 2006. Textbook of Internal Medicine. Pharmacotherapy on glycemic control of type 2 diabetes mellitus. Editor Aru W. Sudoyo et al. 3rd volume. 4th Edition. Jakarta: Publishing Center of the Department of Internal Medicine, Faculty of Medicine, University of Indonesia.

[11] Suryono, 2004. Management of Diabetes Mellitus. Jakarta: Faculty of Medicine Publishing Center

[12] Suryono, S., 2006. Diabetes Mellitus in Indonesia. Jakarta: Publishing Center Department of Internal Medicine FKU.

[13] Tjokroprawiro Askandar, 2001. Diabetes Mellitus: Classification of Diagnosis and Therapy. Jakarta : Gramedia.

[14] Wilhiam, Skach, MD, et al. 1996. Guide to Medical Therapy (Hannd Book Of Medical Treatment). edition 18. Jakarta : EGC.

[15] Sukarta Yusuf. 2013. Anti Diabetes Report. Gajah Mada University. Yogyakarta

[16] Yoco.2014. Antidiabetic Pharmacology Report. University of Indonesia. Jakarta