An Effect Of Methanol Extract Sunkist Orange Peel (Citrus Sinensis (L.) Osbeck) On Blood Sugar And Cholesterol Levels Wistar Rats (Rattus Norvegicus) Induced By Aloxan

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Abstract
Insulin resistance is a condition with damage to target organs that generally respond to the activity of the hormone insulin. About 10% of the population in big cities in Indonesia suffer from insulin resistance. At the cellular level, insulin resistance can result from damage to the pre-receptor, receptor, or post-receptor. The most common cause of insulin resistance is post-receptor damage, namely disruption and damage to insulin signaling pathways. To find out that the methanol extract of Sunkist orange peel can reduce blood sugar levels in Wistar rats. This research uses the experimental laboratory method in vivo with the chosen research design form, namely True Experimental Pre Test and Post Test Control. The Kruskal Wallis test showed that the Sunkist Orange Peel Methanol Extract resulted in a significant decrease in blood sugar levels of Wistar rats with a p-value <0.05, and also the Anova test showed that the Sunkist Orange Peel Methanol Extract resulted in a decrease in blood sugar levels of Wistar rats, which is significant with p-value <0.05. All doses tested affect lowering blood sugar levels, namely, 300 mg/kg BW, 450 mg/kg BW, and 600 mg/kg BW.

Keywords: *Hormone Insulin, Damage Organ, and Blood Sugar*

I. INTRODUCTION

Insulin resistance is a condition with damage to target organs that generally respond to the activity of the hormone insulin. The incidence of insulin resistance in the white population is 3-16%, 2% lower than in Japan. About 10% of the people in big cities in Indonesia suffer from insulin resistance(1). Insulin resistance is the underlying cause of chronic diseases such as diabetes mellitus, which has high morbidity and mortality rates. Insulin resistance is when the insulin hormone secreted by pancreatic -cells cannot produce the desired biological effects in various human body tissues, especially in mediating glucose uptake to adipose tissue, skeletal muscle, liver, and kidneys. (2).At the cellular level, insulin resistance can result from damage to the pre-receptor, receptor, or post-receptor. Disorders in receptors occur because of anti-receptor autoantibodies or other abnormal molecules that interfere with insulin binding to its receptors. In addition, it can also be due to a mutation in the gene encoding the insulin receptor so that the number of receptors is reduced. Disruption of the receptor level occurs due to decreased attraction and sensitivity of the receptor to its binding to insulin. The most common cause of insulin resistance is post-receptor damage, namely disruption and damage to insulin signaling pathways.

The IRS-phosphoinositol kinase pathway cannot function properly. (3).Citrus or citrus is one of the plants that contain vitamin C. Orange peel contains many chemical compounds which are secondary metabolites, namely saponins, essential oils, steroids, flavonoids, and citronella. Pectin, with a high content in citrus, has benefits for lowering blood glucose and cholesterol. Utilization of Citrus sinensis (L.) Osbeck or commonly called Sunkist orange peel as an anti-diabetic is still little done, so it is interesting to do activity testing and prove whether the methanol extract of Sunkist orange peel (Citrus sinensis(L.) Osbeck) can affect blood sugar levels in Wistar rats (Rattus norvegicus) induced with alloxan(4). Orange peel has been studied by many researchers, especially Sunkist orange peel (Citrus sinensis), to prove the effects of Sunkist orange peel on health, including antibacterial, antioxidant, and anti-inflammatory which can be adjusted with

ascorbic acid, ciprofloxacin, and aspirin, respectively. This may be related to the flavonoids, alkaloids, steroids, saponins, and tannins in Sunkist orange peel extract. (5). Based on the background, the problems in the research can be formulated.

II. LITERATURE REVIEW

2.1. Insulin.

Insulin is produced by the pancreas and is a hormone that is the primary key in the process of glucose metabolism from food that enters the human body. Then it is distributed into the blood and body cells, which are used as energy sources. All types of carbohydrates can be converted into glucose in the blood. Insulin helps glucose to carry out metabolism in cells. Patients who experience impaired insulin production are not only people with type 1 diabetes mellitus (DM), but type 2 diabetes also experience impaired insulin production where cell sensitivity decreases under certain conditions. Insulin is grouped based on its ability to maintain blood sugar levels and the speed at which the drug acts to cause an effect. Several types of insulin work quickly after being injected into the blood. This type of insulin is used just before a meal. Then there is a type of insulin with a fast action called short-acting insulin, which aims to lower blood sugar quickly.This type is consumed 30-60 minutes before eating. Usually called insulin lispro and insulin aspart. Then there is the moderate-acting type of insulin, called isophane insulin or zinc insulin. Insulin that works for a full day and is used once a day at night is called long. Insulin is better given by injection because it is less effective when given orally. Insulin is available in flex pen packaging, a unique pen-shaped device used using a special needle.

The insulin pen is the most commonly used form of insulin packaging today because of its patient-friendly use, flexibility for carrying and repeated use, and easy dosing. Insulin must be used correctly and appropriately to produce optimal therapeutic effects(6).Insulin resistance is a condition in which the beta cells of the pancreas cannot secrete insulin, so they cannot produce the biological effects needed by various human body tissues, especially in evenly distributing glucose uptake into adipose tissue, liver, muscle, and kidney. (2). Insulin resistance is a condition associated with the failure or inability of target organs under normal conditions to respond to the activity of the hormone insulin. At the cellular level, insulin resistance can be caused by damage to several groups, namely pre-receptors, receptors, and post-receptors. Pre-receptor disorders occur due to autoreceptors, anti-antibodies, and other abnormal molecules that interfere with insulin binding to its receptors. In addition, it can also be caused by mutations in the gene encoding insulin receptors, causing the number of receptors to decrease. Disturbances at the receptor level occur because of a decrease in the affinity and sensitivity of the receptor for its binding to insulin. The most common cause of insulin resistance is damage to post receptors, namely damage and disruption of insulin signaling pathways. The IRS-phosphoinositol kinase pathway cannot function as intended. This damage affects the failure of GLUT-4 translocation and a decrease in the ability of glucose uptake by cells(7).

2.2. Diabetes

Diabetes mellitus is a chronic disease caused by the inability of the pancreas to produce insulin, characterized by increased blood sugar levels that exceed average values. Diabetes mellitus is one of the metabolic disorders which is usually characterized by hyperglycemia with no symptoms. But the symptoms that need to be observed as signs of Diabetes mellitus are polyuria, polydipsia, and polyphagia with urine that is typical of people with diabetes mellitus, namely the urine tastes sweet. (4).The results of the 2018 Riskesdas data show that the prevalence of Diabetes mellitus in Indonesia for 15 years is 2%. This figure has increased compared to the prevalence of Diabetes mellitus with the results of Riskesdas 2013 of 1.5% in the population 15. However, according to the effects of blood sugar examinations, there was an increase in the prevalence of Diabetes mellitus, from 6.9% in 2013 to 8.5% in 2018. This figure shows that around 25% of people with diabetes have just discovered they have Diabetes. (8).Causes of increased blood sugar levels can be the basis for the classification of Diabetes Mellitus:

1. Type 1 diabetes

This type is increased blood sugar levels is caused by no insulin production at all because the beta cells of the pancreas are damaged

2. Type 2 diabetes

This type causes an increase in blood sugar levels due to a combination of insulin resistance and dysfunction of insulin secretion by B-cell insulin(9).

2.3. Clinical Symptoms

Clinical symptoms in diabetes mellitus can be distinguished according to the types, namely:

1. The classic symptoms of Type I DM that most patients complain about are polyuria, polyphagia, polydipsia, weight loss, fatigue, irritability, and pruritus (itching that occurs on the skin). Patients usually appear emaciated and experience spontaneous, life-threatening ketosis that requires immediate emergency insulin replacement. No autoimmune markers such as the C-peptide chain were found(10).2. Clinical symptoms that are often complained of in Type 2 DM are almost non-existent. Type 2 diabetes often goes unnoticed, and management is only carried out several years after the disease has progressed and complications have occurred. Patients with Type 2 DM are most susceptible to infection, difficult to recover from wounds, decreased vision, and generally have other metabolic syndrome disorders such as obesity, hypertension, hyperlipidemia and detectable C-peptide chains and complications in blood vessels and nerves.(10).

2.4. Metformin

Metformin belongs to the biguanide class of antihyperglycemic drugs, where this drug is widely used for control therapy in type 2 Diabetes Mellitus. Metformin works to make the concentration of blood glucose levels decrease without causing hypoglycemia. The main mechanism of action of metformin is by lowering glucose levels with the aim of causing a decrease in gluconeogenesis in the liver. Phosphorylation of the CREB protein reduces the expression of genes for gluconeogenesis and reduces free fatty acids as a result of substrate gluconeogenesis. Metformin also increases insulin-mediated glucose uptake in peripheral tissues. Metformin is absorbed from the gastrointestinal tract. Metformin absorption is not ideal when taken with meals. Metformin is excreted unchanged and in the absence of metabolic products in breast milk and urine. The dose of metformin tablets used is 200-500 mg 2 times a day every 8 hours. The most common side effects experienced when using metformin as monotherapy are gastrointestinal disturbances such as nausea, vomiting, diarrhea, and abdominal pain.(16).

2.4.1. Wistar Rat (Rattus norvegicu) Experiment Animal

Rats are nocturnal animals whose activities mostly occur in the early morning and evening. Experimental animals that are usually used for scientific research are Wistar rats (Rattus norvegicus). This type of rat is an animal that is considered healthy and suitable for research. The morphology of the Wistar Rat is that it weighs 150-600 grams, has a blunt nose and a large body with a body length of about 18-25 cm, the head and body are shorter than the tail, and small ears and no more than 20-23 mm.(17).

The following is a classification of Rattus norvegicus, namely:(17):

Kingdom : Animalia
phylum : chordates
Class : Mammals
Order :Rodensi
Family : Muridae
Genus :Rattus
Species :*Rattus norvegicus*

III. METHODS

The type of research is experimental laboratory in vivo with the chosen research design form, namely True Experimental Pre Test and Post Test Control and study was conducted in January 2022 – completed The independent variable in the study was the dose of Sunkist Orange Peel Extract (Citrus sinensis (L.) osbeck) which consisted of 300mg/kgBW, 450mg/kgBW and 600mg/kgBW.

The dependent variable in this study is :

- Activity of methanol extract of sunkist orange peel (Citrus sinensis (L.) osbeck) as antidiabetic in female wistar (Rattus norvegicus) rats.

- Activity of methanol extract of Sunkist orange peel (Citrus sinensis (L.) osbeck) as anticholesterol in female wistar (Rattus norvegicus) rats.

IV. RESULTS

4.1 Extract Characteristics

The characteristics consist of weight of fresh simplicia, weight of simplicia powder, Solvent Volume, Extract Weight and Yield which can be seen from the table below.

Table 1. Characteristics of Sunkist Orange Peel Methanol Extract

Character	Score
Simplicia Powder Weight (grams)	273.93
Solvent Volume (Liters)	6.25
Extract Weight (grams)	61.3

The characteristics of the extract used in this study were the weight of the simplicia powder used to make the extract, which was 273.93 grams, the volume of the solvent used was 6.25 liters, and the weight of the finished extract was 61.3 grams.

4.2 Phytochemical Screening

The results of the phytochemical screening prove that there are flavoinoids, phenolics, trapenoids, tannins, alkaloids and saponins. In the table below can be seen the results of phytochemicals from simplicia Orange Peel.

Table 2. Results of Phytochemical Screening of Sunkist Orange Peel Methanol Extract

Phytochemicals	Reactor	Interpretation
Flavonoids	Pb(CH3COO)2	+ + + + +
	Alkaline(NaOH)	+ + +
	Synode Test (Mg+HCl)	+ + +
Phenolic	FeCl3	+
Alkaloids	Mayer	-
	Dragendor	-
Trapeoids/Steroids	Lieberman-Burchard	+ + +
	Salkowski	+ + +
Tannins	FeCl3	+ + + +
Saponins	Foam Test	-

Information : (+) = Contains Compound

(-) = Does Not Contain Compounds

The results of phytochemical screening showed that Sunkist Orange Peel Methanol Extract (EMKS) contained flavonoids, phenolics, alkaloids, trapeoids/steroids, tannins and saponins.

4.3. Blood Sugar Level

A descriptive analysis was carried out in each group to determine whether there was an effect of giving sunkist orange peel extract (Citrus sinensiss (L.) osbeck) on reducing blood sugar levels in wistar rats (Rattus norvegicus) with alloxan-induced hyperglycemia conditions.

Table 3. Results of Average Blood Sugar Levels of Wistar Rats

Group	Blood Sugar Level (mg/dl)			
	Before Alloxan	After Alloxan	7th Day Treatment	14th Day Treatment
Negative	118.20±6.02	146.60 ± 5.60	142.20 ± 4.21	140.00 ± 5.79
Positive	95.40 ± 3.36	150.00 ± 4.47	129.80±5.12	116.20 ± 5.02
P1	83.40 ±7.16	151.60±4.83	120.20±6.30	115.20±5.76
P2	103.00 ± 3.08	152.40 ± 7.06	142.80 ± 6.69	118.60 ± 2.30
P3	90.20±1.30	153.00 ± 8.80	115.20±10.26	117.40 ± 5.18

From the table data above, it shows an increase in blood sugar levels after alloxan induction where alloxan is a diabetogenic substance that has toxic properties to pancreatic beta cells. Then there was a significant decrease in blood sugar levels in the positive group due to the administration of metformin which

is a binguanide antihyperglycemic drug that works by decreasing gluconeogenesis and increasing insulin-mediated glucose uptake in peripheral tissues. In the group giving Metformin and EMKS, there was a decrease in blood sugar levels. In the group giving EMKS at a dose of 300 mg/KgBW and 600 mg/KgBW, it was found that blood sugar levels decreased significantly from the first to the 7th day, the same as when metformin was given. On day 7 to day 14 there was a decrease in blood sugar levels in the EMKS group with a dose of 300 mg/KgBW, but an increase in blood sugar levels in the EMKS administration at a dose of 600 mg/KgBW. Meanwhile, on the first day until the 7th day in the group giving EMKS at a dose of 450 mg/KgBB, there was a slight decrease in blood sugar levels compared to days 7 to 14.

Normality test was performed using Shapiro-Wilk on blood sugar level data in each group of wistar rats (Rattus norvegicus) because the number of samples used in this study was less than 50.

Table 4. Normality Test

Group	P value			
	Before Induction	After Induction	7th day treatment	14th day treatment
Negative	0.79	0.55	0.48	0.89
Positive	0.44	0.80	0.49	0.74
P1	0.20	0.51	0.96	0.74
P2	0.33	0.69	0.75	0.69
P3	0.97	0.33	0.86	0.50

From the results of the Shapiro-Wilk test obtained from data on blood sugar levels of each group of wistar rats, the p value > 00.05 which means that the data on the blood sugar levels of rats in each group has a normal distribution. So based on these results, it was followed by a parametric test using the Anova test to determine whether there was an effect of EMKS on decreasing blood sugar levels of wistar rats with variations in doses of P1 (EMKS 300 mg/KgBB), P2 (EMKS 450 mg/KgBB), P3 (EMKS 450 mg/KgBB), 600 mg/KgBW).The weight of the rats was measured in each group to show that there was no effect of weight on the increase in blood sugar in wistar rats (Rattus norvegicus).

Table 5. Average and Standard Deviation of Body Weight Wistar Rats (Rattus norvegicus)

Treatment Group	Weight (grams)	P value
Negative Group	219.00 ± 21.26	0.28
Positive Group	231.60 ± 12.92	0.84
Sunkist Orange Peel Methanol Extract 300mg/KgBB	224.80 ± 8.29	0.82
Sunkist Orange Peel Methanol Extract 450mg/KgBB	214.00 ± 12.83	0.39
Sunkist Orange Peel Methanol Extract 600mg/KgBB	2218.60 ± 21.61	0.25

From the results of the normality test found in the body weight of each group of wistar rats, the p value > 00.05, which means that the weight data of rats has a normal distribution. There was no significant difference in body weight between all treatment groups, with the weight range of rats used in this study was 200-250 grams. Wistar rats weight criteria are normal with an average of 264 grams(18).

4.4. Comparison between each treatment group

A comparison of the effect of the extract on blood sugar levels was carried out using the Tukey HSD test, which can be seen in the following table.

Table 6. Results of ANOVA Test on Blood Sugar Levels

Treatment Group	Blood Sugar Level, mg/dl [Mean±SD]			
	Before Induction	After Induction	7 days after treatment	14 days after treatment
Negative Control	118.20±6.02	146.60 ± 5.60	142.20 ± 4.21	140.00 ± 5.79
Positive Control	95.40 ± 3.36	150.00 ± 4.47	129.80±5.12	116.20 ± 5.02
Extract 300mg/KgBB	83.40 ±7.16	151.60±4.83	120.20±6.30	115.20±5.76
Extract 450mg/KgBB	103.00 ± 3.08	152.40 ± 7.06	142.80 ± 6.69	118.60 ± 2.30
Extract 600mg/KgBB	90.20±1.30	153.00 ± 8.80	115.20±10.26	117.40 ± 5.18
P value	0.00*	0.53	0.00*	0.00*

From the results of the ANOVA test found in the blood sugar levels of wistar rats between the treatment groups after induction, a p value> 0.05 was obtained, which means there was no difference between the treatment groups, while the treatment group was on before induction, on day 7 and day 14 after administration. EMKS with p <0.05, which means there is a difference between the treatment groups.

4.5. Discussion

Flavonoids are excellent reducing compounds that work both enzymatically and non-enzymatically as inhibitors of many oxidation reactions. Flavonoids act as a good container for superoxide and hydroxy radicals so that they function to protect the damage reactions to lipid membranes(19). Flavonoids act as scavengers of hydroxyl free radicals (OH) because they have antioxidant activity through their redox properties and act as reducing agents, hydrogen donors, and have metal chelating potential.(20). Antioxidants can be given as an effort to inhibit the production of intracellular free radicals and also increase the ability of defense enzymes against free radicals to prevent the emergence of vascular complications related to diabetes and oxidative stress.(21).Flavonoids also have a protective effect on pancreatic beta cells which have a role in producing insulin and can increase the sensitivity of insulin receptors on body cells as a return of pancreatic beta cell function. The antioxidant properties of flavonoids can reduce the activity that occurs in pancreatic beta cells, namely the apoptosis process without disturbing the properties of these cells.(22). Flavonoids can modulate the metabolism of lipids, improve insulin resistance, glucose abnormalities and reduce diabetes complications that occur by insulin resistance and abnormalities of the lipid profile. The benefit of the action of flavonoids is through their ability to improve tolerance and prevent absorption of glucose.

This then stimulates the uptake of glucose from peripheral tissues, acting on the mechanisms of insulin signaling that aim to mimic insulin and regulate the expression and activity of enzymes involved in carbohydrate metabolism pathways. Flavonoids can cause an increase in cAMP due to the inhibition of phosphodiesterase which is inhibited by flavonoids in pancreatic beta cells.(23).In addition to flavonoids, it turns out that the alkaloids found in EMKS also have an important function in reducing blood sugar levels in white rats. These compounds act as alpha glycosidase inhibitors, where the enzyme plays an important role in the process of breaking down polysaccharides into monosaccharides when absorbed in the duodenum. Saponins can also trigger the regeneration of pancreatic beta cells which will cause an increase in the number of active pancreatic beta cells in insulin production, causing a decrease in blood sugar levels in wistar rats. saponin cells together with quiescent cells in the pancreas (where these cells have the ability to regenerate) trigger the regeneration process rather than pancreatic beta cells(22).Based on the results of an in vitro study studied by Cicilia et al, the extract of kaffir lime peel for the application of DM therapy found that the extract showed inhibition of the performance of the -amylase enzyme which is an antidiabetic activity in converting starch into glucose. Another study, namely grapefruit (Citrus maxima) conducted by Peace et al, where administration of the extract in a dose of 600mg/kgBW showed potential as a diabetes controller and also works in lowering cholesterol.(24).

V. CONCLUSION

From the research that has been done to see whether there is an effect of Sunkist Orange Peel Methanol Extract on changes in Blood Sugar and Cholesterol Levels of wistar rats, it can be concluded that:

1. Sunkist Orange Peel Methanol Extract contains flavoinoids, phenolic compounds, trapenoids, tannins, alkaloids and saponins.
2. There is a significant increase in blood sugar levels after alloxan induced
3. Sunkist Orange Peel Methanol Extract has a significant effect in reducing blood sugar levels of wistar rats, it can be seen from the results of the analysis, namely the Anova test in statistical tests. All groups of EMKS dose variations were effective in reducing blood sugar levels of wistar rats.
4. There were differences in cholesterol between all treatment groups.

REFERENCES

[1] Ulfa M, Sakinah EN, Sudarmanto Y, Firdaus J. Effects of Cassava Resistant Starch (Manihot esculenta Crantz) on the HOMA-IR and HOMA-B indices of Diabetes Model Rats. Health Library. 2020;7(1):1.

[2] Anas Y, Fithria RF, Nuria MC, Martha A, Nugroho AE, Astuti P. ANTIDIABETIC ACTIVITY OF n-HEXAN FRACTION OF ENTHANOL EXTRACT OF ARM LEAVES (Leucas lavandulifolia JE. Smith) IN TYPE-2 DM RATS WITH INSULIN RESISTANCE. ***Kartika J Ilm Farm.*** 2015;3(1):20–8.

[3] Sukarno DA. Effect of Physical Exercise on Improvement of Insulin Resistance. ***KELUWIH J Health and Medicine.*** 2021;2(2):110–4.

[4] Mellasari A, S AA, Butar-butar PS, Mutia MS, Lubis EP. RESEARCH ARTICLES Test of Sunkist Orange Peel Extract on Blood Sugar Levels and Structure. 2021;44(4):253–63.

[5] Monograph B. Ethanol extract of sunkist orange peel.

[6] Simamora S, Sarmadi, Mona Rahmi Rulianty, Ferawati Suzalin. Care for Insulin Use. ***Din J Servant to Masy.*** 2021;5(3):638–44.

[7] Muhammad AA. Insulin Resistance And Insulin Secretion Dysfunction As Factors Causing Type 2 Diabetes Mellitus. ***J Public Health.*** 2018;8(2):173–8.

[8] Ministry of Health of the Republic of Indonesia. Stay Productive, Prevent And Overcome Diabetes Mellitus. Indonesian Ministry of Health's data and information center. 2020.

[9] Donelly richard and rudy bilous. DIABETES HANDBOOK. Medical Books; 2015.

[10] Inayati I, Qoriani HF. An expert system for early detection of diabetes mellitus (DM) based on Android. ***JLink.*** 2016;25(2):10–5.

[11] Extract M, Orange K, Level T, Blood G, Wistar T, Streptozotocin I. A Study on the Benefits of Orange Peel Extract on Blood Sugar Levels in Wistar Mice with Hypercholesterolemia Induced by Streptozotocin.

[12] Antioxidant K, Health B. Sunkist Orange Peel Extract.

[13] Endah SRN. MANUFACTURING OF ETHANOL EXTRACTS AND Phytochemical Screening ETHANOL EXTRACTS OF SYNTOCK SKIN (Cinnamomun sintoc Bl.). ***J Hexagro.*** 2017;1(2):29–35.

[14] Leksono WB, Pramesti R, Santosa GW, Setyati WA. Types of Methanol and N-Hexane Solvents Against Antioxidant Activity of Gelidium sp. Seaweed Extract. From Drini Beach Gunungkidul – Yogyakarta. ***J Tropical Marine***. 2018;21(1):9.

[15] Yuliastuti D, Sari WY, Muna N, Tengah J. Effect of longan fruit juice administration on alloxan-induced blood sugar levels in mice. ***J Pharmacist*** Vo. 2020;9(2):131–8.

[16] Gumantara MPB, Oktarlina RZ, Pharmacology B, Medicine F, Lampung U. Comparison of Monotherapy and Sulfonylurea-Metformin Combination Therapy for Patients with Type 2 Diabetes Mellitus. Comparison of Monotherapy and Sulfonylurea-Metformin Combination Therapy to Patient with Type 2 Diabetes Mellitus. Majority. 2017;6(1):55–9.

[17] Danthy R, Rakanita Y MS. Test the Effect of Purple Eggplant Skin Ethanol Extract on Blood Glucose Levels in Hypercholesterolemic-Diabetic Mice. ***Farmakol J Farm.*** 2019;XVI.

[18] Noordam ER, Tamat SR, Syamsudin S. Anti-Obesity Activity of Tin Leaf Extract (Ficus carica Linn) in Rats Given a High Fat Diet. ***J Indonesian Pharmaceutical Sciences***. 2019;17(1):81.

[19] Ginting CN. Rubber Leaves Benefits for Health [Internet]. Medan: Prima Indonesia University. 2020. 1–139 p. Available from:file:///C:/Users/USER/Downloads/1139-Article Text-2555-1-10-20200718.pdf

[20] Ginting CN, Lister INE, Girsang E, Riastawati D, Kusuma HSW, Widowati W. Antioxidant Activities of Ficus elastica Leaves Ethanol Extract and Its Compounds. Mol Cell Biomed Sci. 2020;4(1):27.

[21] Prawitasari DS. Schleiss, MR, 2007. Infectious Disease: Antibiotic Therapy. Nelson Textbook Of Pediatrics. 18th ed. Elsevier. 2019;1(1):47–51.

[22] Valentino A, Gunawan R, Wiranto, Simatuang Febyami n, Baringbing miranda s, Girsang E, et al. The effectiveness of bark ethanol (Salacca zalacca) on weight loss and blood sugar levels of white rats (Rattus norvegicus). ***J Medicine and Health Sciences.*** 2018;8(3):279–85.

[23] Azzahra A, Farhani N, Syahfitri W, Pasaribu SF. Potential Flavonoid Content in Bajakah Wood as Antidiabetic. ***J Tambusai Educator.*** 2022;6:14345–50.

[24] Depari SAF, Rambe DJA, Meilando R, Lisya C, Mutia MS, Lubis YEP. Effectiveness Test of Ethanol Extract of Sunkist Orange Peel (Citrus sinensis (L.) Osbeck) Against Blood Sugar Levels of Wistar Rats (Rattus norvegicus) With Streptozotocin Induced Hypercholesterolemia. Biospecies. 2021;14(1):1–9.