THE INDONESIAN JOURNAL OF MEDICAL LABORATORY TECHNOLOGY
https://jurnal.stikesbanyuwangi.ac.id/index.php/IJ-CALORY
Volume 1, No. 1, January 2024 (Page. 20-27)

The Effect Of Administering Herbal Extract Of Sambiloto Leaves (Andrographis Paniculata) On Blood Sugar Levels In Male White Rats (Rattus Norvegicus) Induced By Aloksan

Leny Eka Tyas Wahyuni*[a]| Nur Rezky Khairun[a]
[a] Study Program of Pharmacy, Universitas Mulawarman, Indonesia
*Corresponding Author: *lenyekatyas@farmasi.unmul.ac.id*

No HP Author: +62 82244099040

ARTICLE INFORMATION

Article history
Received (21st December 2023)
Revised (04th December 2023)
Accepted (22nd January 2024)

Keywords
Andrographis paniculata,
Andrographolide,
Na-CMC

ABSTRACT

Introduction*: Diabetes mellitus is a chronic disease characterized by hyperglycemia, namely high levels of sugar in the blood. This condition occurs due to a disruption in the production or function of insulin in the body , or both. Currently, people prefer alternative treatments using herbal medicines because they have few side effects and are easy to obtain both in terms of price and availability. Sambiloto (Andrographis paniculata Ness) is a traditional medicine used by Indonesians to lower blood glucose because it contains andrographolide and flavonoids.*
Objectives and Methods*: This study aims to determine whether bitter leaf herbal extract has an anti-diabetic effect on male diabetic white rats (Rattus norvegicus). This study used a pretest-posttest control group design. The ingredient used is bitter leaf extract. Subjects were 25 mice divided into five groups, namely P1 (Na-CMC 0.5%), P2 (metformin 45 mg/kgBB), P3 (extract 100 mg/kgBB), P4 (extract 200 mg/kgBB), and P5 (400 mg/kgBB extract).*
Results*: One Way ANOVA test showed significant differences in the five treatment groups with p = 0.000 (p<0.05). The LSD post hoc test showed that there was a significant difference between P3 and P1, P2, and P5 and not significantly different from P4.*
Conclusions*: Based on research results, bitter leaf extract (Andrographis panicula) 400 mg/kgBB can significantly reduce blood glucose levels in male rats (Rattus norvegicus)*

Introduction

Diabetes mellitus (DM) is a chronic disease characterized by hyperglycemia, namely high levels of sugar in the blood. This condition occurs due to a disruption in the production or function of insulin in the body, an important hormone responsible for regulating blood sugar levels. Chronic hyperglycemia in the case of diabetes can cause various serious complications, including damage to vital organs such as the heart, kidneys, and eyes. It can lead to organ dysfunction or failure (Ginanjar, 2014).

The World Health Organization (WHO) has identified that the number of people suffering from type 2 DM is expected to continue to increase globally, placing this condition as one of the main challenges in the field of public health worldwide. In Indonesia, this situation is also worrying, where WHO projects that the number of DM sufferers will increase from 8.4 million people in 2000 to around 21.3 million people in 2030. Furthermore, there is estimated to be a significant increase of up to 2-3 double by 2035. This is in line with predictions from the International Diabetes Federation (IDF), which also shows an alarming increasing trend in the

incidence and prevalence of DM in Indonesia, from 9.1 million in 2014 to an estimated 14.1 million in 2035 (PERKENI, 2019). Especially in East Java Province, there was a very significant increase in the prevalence of diabetes mellitus, namely 329.8%, in the last two decades, placing this province in sixth place out of ten provinces with the highest prevalence of diabetes in Indonesia, 2.1%, figures which is much higher than the national average of 1.5% (DINKES Jatim, 2018).

As public awareness of maintaining health and seeking more natural treatment alternatives increases, herbal medicine is becoming increasingly popular. Herbal medicines, which come from plants or their extracts, are claimed to be effective treatment options and have a lower risk of side effects. Herbal medicine is not only used to treat certain diseases but is also often used for preventive purposes and to increase the body's immunity (Lau, 2019).

Sambiloto (Andrographis paniculata Ness) is an herbal plant that has long been known and used by Indonesian people as an alternative treatment, especially in lowering blood glucose levels. Bitter leaves are rich in bioactive compounds such as polyphenols, orthosiphon glucose, essential oils, saponins, flavonoids, saponins, potassium salts, myoinositol, andrographolide. The andrographolide compound contained in Sambiloto has been proven to have a positive effect in increasing glucose use by muscles in rats suffering from diabetes through the GLUT-4 transporter stimulation mechanism, which in turn can reduce glucose levels in blood plasma (Lindawati, 2016). Apart from that, the bitter extract also has the potential to stimulate insulin release and inhibit glucose absorption in the body by inhibiting the enzymes *alpha-glucosidase* and *alpha-amylase* (Sukmawati, 2016).

Based on this, researchers were interested in conducting this research to test the anti-hyperglycemic activity of bitter leaf on male white rats (*Rattus novergicus*).

Material and Methods

The This research is accurate experimental research using a Pretest-Posttest Control Group Design. The research was carried out in May 2021 in the Clinical Pathology laboratory, STIKES Banyuwangi. The research subjects were 25 male white rats (Rattus norvegicus), which were divided into five groups, namely:

1. Group I (negative control) will be given Na-CMC 0.5%. This group determines primary conditions without the influence of drugs or special treatment.
2. Metformin will be given to Group II (positive control). This group compares standard treatments that have been proven effective in some instances.
3. Groups III, IV, and V (treatment groups) will be given bitter leaf extract at 100 mg/kg BW, 200 mg/kg BW, and 300 mg/kg BW, respectively. The aim of administering different doses was to evaluate the effect of graded doses of bitter leaf extract on the variables measured.

Measurements were carried out before and after treatment to see the differences due to the intervention. In the initial stage, all mice will have their basic parameters measured. After that, they will receive treatment according to their respective groups for the specified period. At the end of the period, all mice will be measured again to see the changes. The data obtained will then be analyzed statistically to determine the significance of the differences between the control and treatment groups. Thus, this research can provide valid information regarding the effects of bitter leaf extract on the measured parameters and contribute to future science and clinical applications.

1. Material

a. Tool

The tools used were rat cages, oral probes, digital scales, glucometers, glucose strips, stopwatches, scalpels, disposable syringes, mortar pestles, measuring cups, stir sticks, rotary evaporators, gloves, masks, cutting boards, glass jars.

b. Material

The ingredients used are bitter leaf extract (Andrographis panicula), metformin, alloxan, 0.5% Na-CMC solution, 70% alcohol, distilled water, cotton, and test animal feed.

2. Methods

a. Making Sambiloto Leaf Extract

The bitter leaf extract used in this research was obtained through an extraction process using the maceration method using 96% ethanol solvent. The extraction process is carried out in the Natural Materials laboratory, which is equipped with modern equipment and meets laboratory standards. The bitter leaf, the main ingredient for this research, was obtained from the Purwoharjo area, Banyuwangi Regency, which is famous for the quality of its medicinal plants. A total of 5 kg of fresh bitter leaf was collected from a well-managed garden. After that, wet sorting is carried out to separate leaves that are damaged or unfit for use, and the leaves are washed thoroughly with running water to remove dirt and dust stuck to them. Next, the bitter leaf is air-dried for three weeks. The drying process is carried out in a shady place and protected from direct sunlight to prevent damage to the active compounds contained in the leaves. After the leaves are completely dry, dry sorting is carried out to ensure that only good-quality leaves are used. The bitter leaf simplicia is then crushed by kneading until small and coarse particles are formed, which allows the 96% ethanol solvent to penetrate well during the maceration process.

The prepared Simplicia powder is then macerated using 96% ethanol for several days to extract the active compounds contained in the bitter leaf. The macerate obtained from the maceration process is filtered using filter paper to separate the liquid from the solid residue. The liquid obtained is then concentrated using a rotary evaporator, a tool that evaporates the solvent to obtain a thick extract of bitter leaf with a high concentration. This thick extract of bitter leaves was then used to test its effects on male white rats. Tests were carried out according to the previously described research design, with the aim of evaluating the potential benefits and side effects of bitter leaf extract on male white rats. Hopefully, this research results will provide valuable scientific information for developing bitter-leaf-based herbal medicines.

b. How to Take Blood Samples

Blood glucose levels are the amount of glucose in blood plasma. Rat blood is taken by cutting the rat's tail 1 cm from the base of the tail, massaging until the blood comes out, and dripping it onto a glucose strip.

c. Making Alloxan Solution

The dose of alloxan given to make rats hyperglycemic is 150 mg/kgBW intraperitoneally. If the rat's body weight is 200 grams, then 30 grams of alloxan is given. Alloxan monohydrate powder is weighed at 1.2 grams and then dissolved with sterile distilled water for injection to 100 mL.

d. Preparation of 0.5% Na-CMC Solution

Na-CMC was weighed at 0.5 grams and dissolved in distilled water to 100 mL.

e. Making Metformin Solution

The dose of metformin given to mice was 45 mg/kgBW. Metformin powder weighed as much as 360 mg and was then suspended in a 0.5% Na-CMC solution to 100 mL.

f. Making Test Solutions

The dosage of bitter leaf extract is 100 mg/kgBB, 200 mg/kgBB, and 400 mg/kgBB. The bitter leaf extract was weighed as 0.8 grams (dose 100 mg/kgBW), 1.6 grams (dose 200 mg/kgBW), and 3.2 grams (dose 400 mg/kgBW), then suspended in 0.5% Na-CMC up to 100 mL.

g. Test Animals

The test animals used were white rats (Rattus norvegicus). The inclusion criteria were males, a body weight of 150-250 grams, and healthy rats characterized by active activity. The exclusion criteria were rats that had wounds, defects, or died before and during treatment.

h. Data analysis

All data obtained were analyzed using the Statistical Package for Social Sciences (SPSS) computer program. The analysis results were conducted to see whether the distribution was statistically normal using the Shapiro-Wilk test ($p>0.05$) because the sample size was $n\leq50$. The data showed that it was usually distributed ($p>0.05$), so it was continued with the parametric one-way analysis of variance (ANOVA) test. Then, proceed with the Post Hoc Test Least Significant Difference (LSD) to see the differences between treatment groups.

Results and Discussion

Table 1. Measurement of Rat Blood Glucose in Each Group

Treatment	Blood glucose levels (Mg/dl)				
	D_0	D_1	D_2	D_3	D_4
Concentration 100 mg/kg	56,4	498,8	464,2	392,6	392
Concentration 200 mg/kg	60,2	504,8	422	331	308,4
Concentration 400 mg/kg	72	430,4	408,6	272	213,6
Positive control	100	488,6	434	303,8	182,4
Negative Control	99,6	544,2	344	118	118,8
Means	77,64	493,36	414,56	283,48	243,04

Before alloxan induction (D0), the mice's blood glucose levels were within the normal range, with an average value of 77.64 mg/dl. This shows that the mice were in a stable health condition and did not experience impaired glucose metabolism. This average value also indicated that no external factors influenced their blood glucose levels before the experiment began. After alloxan (D1) was administered, blood glucose levels in the five groups of mice drastically increased, with an average value reaching 493.36 mg/dl. This increase shows that alloxan has successfully induced significant hyperglycemia in experimental animals. Hyperglycemia is a condition where blood glucose levels exceed normal limits, which can cause various health complications if not treated immediately. After treatment, the mice that received bitter leaf extract at a dose of 400 mg/kg BW showed the fastest reduction in blood glucose levels until they reached normal limits. On the sixth day after administration of the extract, blood glucose levels in this group were recorded with an average value of 119 mg/dl. This indicates that bitter leaf extract at high doses has a robust hypoglycemic effect. The blood glucose levels in this group continued to decrease until the ninth day after treatment, reaching an average of 117.8 mg/dl, which shows the stabilization of the mice's health condition.

Meanwhile, the group of mice that received bitter leaf extract at a dose of 200 mg/kg BW experienced a slighter decrease in blood glucose levels. On the ninth day after treatment, their blood glucose levels reached an average of 183.4 mg/dl. Even though there was a decrease, this value was still higher compared to the group receiving a 400 mg/kg BW dose, indicating that the lower dose had a less effective hypoglycemic effect. These results indicate that administering bitter leaf extract, especially at 400 mg/kg BW, can help reduce blood glucose levels in mice that previously experienced hyperglycemia due to alloxan induction more quickly than at 200 mg/kg BW. This indicates the potential benefits of bitter leaf extract in treating hyperglycemia, especially when given in higher doses. Further research is needed to understand this extract's mechanism of action and determine the optimal dosage that is safe and effective for humans.

The research was carried out in May 2021 at the STIKES Banyuwangi Clinical Pathology Laboratory. The first thing to do was to make bitter leaf extract and prepare experimental animals. The collected bitter leaves were washed and dried in the air for three weeks. Drying aims to reduce the sample's water content, prevent the growth of microorganisms (fungi), and stop enzymatic processes that can trigger sample spoilage. When drying, avoid the sample from

sunlight to prevent damage to the metabolite content, especially andrographolide. The results of drying the sample will form a simplicia. The following process is to reduce the sample size to expand the contact area between the sample and the solvent during extraction to maximize the results obtained. The wider the contact area between the material and the solvent, the greater the effectiveness of the extraction. The following process is to carry out extraction using the maceration method. The maceration method includes an extraction method that uses simple procedures and equipment and does not require heating, which can damage the secondary metabolite content, especially andrographolide (Pradini et al., 2017). The solvent used in the extraction process is 96% ethanol, which has a green appearance and is thicker because it has less water content than the 70% ethanol solvent, so it is not easy for microorganisms to grow. The 96% ethanol solvent attracts fewer compounds in the sample (Husna et al., 2016). As a result of maceration, a thick, bitter leaf extract is obtained, which is green in color and has a bitter taste.

The experimental animals in this research were male white rats (Rattus norvegicus); these rats have relatively fast metabolic abilities and are very sensitive when used in types of research related to the body's metabolic system; male rats are used more often than females because male rats show a shorter growth period. Longer than female and male mice does not affect the hormone cycle, which will later influence the research results (Angria, 2019).

The research was carried out for 19 days, consisting of acclimatization of mice for seven days, then induction of alloxan to diabetic mice for 2-3 days, and treatment of each group for nine days. Rat blood glucose observations were performed five times before alloxan induction, after alloxan induction, and on day 3, day 6, and day nine after treatment. Blood glucose measurements in mice were carried out by cutting the mice's tails ± 1 cm after they had been fasted for 8 hours while still providing them with drinking water. Alloxan induction was carried out intraperitoneally, and it was found that 25 mice experienced an increase in blood glucose levels. The alloxan compound can damage pancreatic β cells by forming a redox cycle of superoxide radicals, which will undergo dismutation to become hydrogen peroxide. The highly stimulated activity of superoxide free radicals then increases the concentration of cytosolic calcium, which causes rapid destruction of pancreatic β cells. Damage to pancreatic β cells will cause a decrease in insulin secretion, which results in the glycogenesis reaction and glucose transport within the cells being reduced and the glycogenolysis process becoming uncontrolled, increasing blood glucose levels in experimental animals (Yusni et al., 2017).

The blood glucose levels of mice before alloxan induction were normal, with a mean value of 76.6 mg/dl; after administration of alloxan, there was an increase in blood glucose in the five groups with an average of 494.8 mg/dl. After treatment, the mice that showed the fastest reduction in blood glucose levels to normal limits were the 400 mg/kg BW bitter leaf extract group on day six after administration of the extract with an average of 119 mg/dl and continued to decrease until day nine after treatment with an average -an average of 117.8 mg/dl. In comparison, 200 mg/kgBB bitter leaf extract decreased blood glucose levels to normal limits on day nine after treatment with an average of 183.4 mg/dl. After the research was conducted, the data was analyzed using SPSS (Statistical Package for Social Science). The first statistical test was the normality test, which aimed to see whether the data distribution was generally distributed in each group. The normality test was the Shapiro-Wilk test because the number of samples used was less than 50. After carrying out the normality test, the data was found to be normally distributed, so the One Way ANOVA parametric test was carried out to find out the effectiveness of bitter leaf extract in reducing blood glucose levels and to find out whether there was a significant difference in each group based on observation time, the results obtained were that there was a significant difference P value 0.000 ($p<0.05$). Based on the test results, the research hypothesis H0 was rejected, and H1 was accepted, namely that there was a decrease in blood glucose levels in male white rats (Rattus norvegicus) that were given bitter leaf extract

(Andrographis paniculata). A decrease in blood glucose levels was seen on days 6 and 9, except on day 3. To find out which groups had significant differences, a post hoc test was carried out, the Least Significant Difference (LSD) test.

The study showed the effectiveness of Andrographis paniculata bitter leaf extract in reducing blood glucose levels in male white rats (Rattus norvegicus). This is due to the theory that the andrographolide compound is the main diterpenoid in bitter leaves and plays a role in reducing blood glucose levels; this compound works to inhibit glucose absorption by inhibiting the enzymes alpha-glucosidase and alpha-amylase (Sukmawati et al., 2016). The andrographolide compound also increases insulin sensitivity and thereby stimulates glucose uptake and oxidation by peripheral tissues, controls abnormal lipid metabolism, and removes free radicals from the circulation that disrupt the integrity of the plasma membrane, resulting in a decrease in the number of efficient plasma membrane receptors or transporter proteins required for uptake—glucose from the bloodstream (Hossain et al., 2014). Apart from andrographolide, bitter also contains paniculides, flavonoids, and farnesols (Nasution et al., 2019). Flavonoids capture and neutralize free radicals such as ROS or RNS to repair damaged tissue, inhibit inflammatory processes, and regenerate cells. Flavonoids also have antidiabetic activity because they can regenerate cells in the islets of Langerhans (Nabatonis et al., 2015).

400 mg/kgBB bitter leaf extract showed a higher ability to reduce blood glucose levels compared to 100 mg/kgBB bitter leaf extract and 200 mg/kgBB bitter leaf extract; this was caused by increasing the dose of bitter leaf extract, which had a good effect on reducing glucose levels blood because increasing the dose increased the number of active compounds contained in the ethanol extract of bitter leaf (Andrographis paniculata) (Nabatonis et al., 2015). These results are based on research that chose a dose of 400 mg/kg of Andrographis paniculata ethanol extract as the dose to be used in research studies. Diabetes (Zhang et al., 2000). Other research also showed that bitter leaf ethanol extract at a dose of 4.4 mg/kgBW showed better improvements, visible boundaries of the Langerhans islets area that were starting to become apparent, there were connections between the Langerhans islets and the acinar, and an increase in the number of cells in the Langerhans islets compared to the treatment group. Ethanol extract therapy of bitter leaves at 2.2 mg/kgBB (Nubatonis et al., 2015).

200 mg/kgBB bitter leaf extract lowered blood glucose levels more quickly than the 100 mg/kgBB bitter leaf extract group, with a mean value on day nine after treatment with the 200 mg/kgBB bitter leaf extract group of 183.4 mg/dl. This is in line with research, which shows that administration of 200 mg/kg bitter leaf extract can significantly reduce glucose levels starting from the first hour and continues to decrease until 7 hours after treatment compared to groups given metformin, 50 mg/kg, and 100 mg bitter leaf extract. Mg/kg (Akhtar et al., 2016). Other research also states that administering ethanol extract of the bitter herb in the glucose tolerance test can reduce blood glucose levels; this is proven by the decrease in glucose in the glucose tolerance test, which increases with increasing dose in the range of 0.5-2.0 g/KgBW (Shofa et al. al., 2017).

The bitter leaf extract group with a dose of 100 mg/kgBW until the day had blood glucose levels that were not yet normal, with a mean value of 213.4 mg/dl; this may be due to the dose not being able to help the reabsorption of other active substances due to the damage to pancreatic β cells which was quite severe so causes glucose levels to rise too high. The levels of the active substance are not yet able to penetrate the pancreatic β cell receptors so that they are not absorbed into the blood circulation, as evidenced by research that shows the results in mice given a dose of 150 mg/kgBB bitter leaf extract did not show a decrease in levels. Glucose was expected after seven days of therapy with a mean value of 305 mg/dl. After 14 days of treatment, the blood glucose levels of the mice returned to normal, with a mean value of 166.8 mg/dl (Alaydrus et al., 2018).

Conclusion

Bitter leaf extract (Andrographis panicula) at doses of 100 mg/kgBW, 200 mg/kgBW, and 400 mg/kgBW had an anti-diabetic effect on male white rats (Rattus norvegicus) induced by alloxan. Bitter leaf extract (Andrographis panicula) 400 mg/kgBW is the most significant dose for reducing blood glucose in male rats (Rattus norvegicus) induced by alloxan.

References

Badan Pusat Statistik Indonesia. (2021). *Luas Daerah dan Jumlah Pulau Menurut Provinsi Tahun 2021*.

Ginanjar E, Rachman AM. Buku Ajar Ilmu Penyakit Dalam. 6th ed. (Setiati S, Alwi I, Sudoyo AW, Simadibrata M, Setyohadi B, Syam AF, eds.). (2014). Interna Publishing.

Tim Penyusun Buku Pedoman Pengelolaan dan Pencegahan Diabetes Mellitus Tipe 2 di Indonesia. Pedoman Pengelolaan Dan Pencegahan Diabetes Mellitus Tipe 2 Dewasa Di Indonesia 2019. (2019). PB PERKENI.

Dinas Kesehatan Provinsi Jawa Timur. (2018). Profil Kesehatan Provinsi Jawa Timur.

Lau SHA, Herman, M R. Studi Perbandingan Tingkat Pengetahuan Masyarakat Tentang Obat Herbal Dan Obat Sintetik Di Campagayya Kelurahan Panaikang Kota Makassar. (2019). *J Farm Sandi Karsa*, 5(1):33-37.

Paramitha MD, Rahmanisa S. Ekstrak Etanol Herba Sambiloto (Andrographis Paniculata) Sebagai Antidiabetik Terhadap Mencit Wistar Terinduksi Aloksan. (2016). Med J Lampung Univ, 5(5).

Lindawati NY, Nugroho AE, Pramono S. The Effect Of Combination From Purified Extract Of Sambiloto Herb (Andrographis Paniculata (Burm.F.) Nees) And Pegagan Herb (Centella Asiatica (L.) Urban) Of Translocation Of Glut-4 Protein In Type 2 Diabetes Mellitus-Insulin Resistance Rats. (2014). Tradit Med J, 19(2). doi:https://doi.org/10.22146/tradmedj.814 2

Sukmawati S, Harsita MA, Kosman R. Uji Efek Hipoglikemik Kombinasi Ekstrak Etanol Daun Sambiloto (Andrographis Paniculata Nees) Dengan Akarbose Pada Tikus Putih (Rattus Norvegicus) Terinduksi Aloksan. (2016). *J Ilm As-Syifaa*, 8(2):75-82. doi:10.33096/jifa.v8i2.203

Pradini SA, Pambudi PPR, Dinah FA. Uji Efek Antidiabetik Kombinasi Ekstrak Etanol Daun Stevia (Stevia Rebaudiana Bert.) Dan Daun Sambiloto (Andrographis Folium) Pada Tikus Jantan Galur Wistar Yang Diinduksi Aloksan The Effect Antidiabetik A Combination Of Extracts Ethanol Leaves Stevia. (2017). *Indones J Med Sci*, 4(2):177-182.

Husna RSN, Effendi EM, Maheshwari H. Efek Samping Ekstrak Etanol 96% Dan 70% Herba Kemangi (Ocimum Americanum L.) Yang Bersifat Estrogenik Terhadap Kadar Asam Urat Pada Tikus Putih. (2016). *Ekol J Ilm Ilmu Dasar dan Lingkung Hidup*, 16(2).

Angria N. Undur-Undur (Myrmeleon Sp.) Sebagai Antidiabetik. (R. SCH, ed.). (2019). Uwais Inspirasi Indonesia.

Yusni Y, Akbar IB, Rezania R, Fahlevi R. Penurunan Kadar Gula Darah Akibat Pemberian Ekstrak Manggis (Garcinia Mangostana) Dan Tomat (Lycopersicum Esculentum Mill) Pada Tikus Diabetes. (2017). Glob Med Heal Commun, 5(1).

Hossain MS, Urbi Z, Sule A, Rahman KMH. Andrographis paniculata (Burm. f.) Wall. ex Nees: A Review of Ethnobotany, Phytochemistry, and Pharmacology. (2014). Sci World J, 2014:1-28. doi:10.1155/2014/274905

Nasution P, Sugito S, Kuswiyanto K. Pengaruh Konsentrasi Ekstrak Metanol Daun Sambiloto (Andrographis Paniculata Ness) terhadap Sensitivitas Enterobacteriaceae dengan Metode Difusi. J Lab Khatulistiwa. 2019;2(1):26. doi:10.30602/jlk.v2i1.323

Nubatonis DC, Ndaong NA, Selan YN. Pengaruh Pemberian Ekstrak Etanol Daun Sambiloto (Andrographis paniculata Nees) Terhadap Histopatologi Pankreas Mencit (Mus musculus) Diabetes Melitus (DM) Tipe I. (2015). J Kaji Vet, 3(1).

Zhang XF, Tan BKH. Antihyperglycaemic And Anti-Oxidant Properties Of Andrographis Paniculata In Normal And Diabetic Rats. Clin Exp Pharmacol Physiol. 2000;27(5-6):358-363. doi:10.1046/j.1440-1681.2000.03253.x

Akhtar M, Bin Mohd Sarib M, Ismail I, et al. Anti-Diabetic Activity and Metabolic Changes Induced by Andrographis paniculata Plant Extract in Obese Diabetic Rats. (2016). Molecules, 21(8):1026. doi:10.3390/molecules21081026

Shofa, Andzar Fikranus, Anny Victor Purba, Siswa Setyahadi. Interaksi Ekstrak Sambiloto (Andrographis paniculata (Burm.F.)Ness) dengan Glibenklamid terhadap Ekspresi Gen CYP3A4 pada Kultur Sel HepG2. (2017). Jurnal Sains Farmasi & Klinis, 4(1).

Alaydrus S, Alifia A, Anam S. Efek Ekstrak Etanol Kombinasi Daun Sambiloto Dan Daun Mimba Terhadap Kadar Glukosa Darah Tikus. (2018). Farmakol - J Farm, 15(1).