Pharmacogn J. 2021; 13(6): 1502-1508
A Multifaceted Journal in the field of Natural Products and Pharmacognosy
www.phcogj.com

Research Article

Antidiabetic Activity and Phytochemical Constituents of *Syzygium cumini Leave* in Kadipaten, Central Java Indonesia, Indonesia

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ABSTRACT

Introduction: Ethnomedicaly, jamblang (java plum) has been used as antidiabetic treatment in Dayak Tribe. This study aims to evaluate the effectiveness and the safety of the jamblang leaf extract as an antidiabetic. **Objective:** Evaluate Effecticity of *Syzigium cumini* (java plum) as anti-diabetic herb. **Method:** The antidiabetic activity test, used an animal model which gaven food a high fat diet High Fat Diet (HFD) then it was induced with Streptozotocin injected intraperitoneally. The subjects used in the study were male rats (*Ratus novergicus*) Sprague-Dawley strain. **Results:** Oral administration of jamblang extract has anti hyperglycemic activity through decrease of fasting blood glucose point significantly (dose 1, 50mg/ Kg Bw p: <0.0001, dose 2, 100 mg/Kg BW p: <0.0001).
Key words: *Syzigium cumini,* Anti-hyperglicemic, Fasting blood glucose.

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History

- Submission Date: 13-08-2021;
- Review completed: 04-09-2021;
- Accepted Date: 06-09-2021.

DOI : 10.5530/pj.2021.13.191

Article Available online

http://www.phcogj.com/v13/i6

INTRODUCTION

Diabetes is spotlighted during the COVID-19 pandemic. This illness is one of the comorbidities in patients with COVID-19. ACE 2, which is known to be a receptor for the COVID-19 virus, is found in many digestive tracts and glands such as the pancreas. So there is a correlational relationship between diabetes, diabetes severity, and COVID-19[1]. Diabetes is characterized by polydipsia, polyurea, ketonemia and ketonuria. Other clinical signs and early symptoms of D. mellitus if left unattended, will lead to diabetes complications such as morbidity and mortality in diabetics. Hyperglycemia is involved in the development of secondary complications in D. mellitus[2].

The prevalence of diabetes increase globally. In 2019, approximately 463 million adults were living with diabetes, then will rise to 700 million by 2045. About 79% of adults with diabetes were living in developing country. In Indonesia, about 10 million people are living with diabetes in 2019 and it is estimated to rise to 16.6 million by 2045. Diabetes is one of major cause of death in Indonesia. Moreover, Indonesia was rated one of top ten countries for number of diabetes[3].

This is compounded by emerging evidence showing that COVID-19 can actually trigger diabetes in healthy people and also cause severe complications from pre-existing diabetes. Clinical observations so far suggest a two-way relationship between COVID-19 and diabetes. On the other hand, diabetes is associated with an increased risk of COVID-19 severity and death. Between 20 and 30% of patients who die with COVID-19 are reported to have diabetes[4]. In the conditions of the COVID-19 pandemic, handling diabetes is a problem that also needs to be highlighted as an indirect implication of this COVID-19 pandemic.

According to certain Note, up to 72.8% of diabetic patients used herbal medicines and other complementary and alternative medicine (CAM)[5]. Many people taking herbal medicines have chronic illness such as diabetes, cancer, or arthritis. Because of their sickness is incurable, they believed that herbal medicines will give them comfort. Patients often take herbs and conventional drugs concurrently. Interaction between them can be dangerous and have serious concern about safety for patients[6].

About eighty percent of world population are using herbal medicines for primary health care especially in developing country. This is because of the belief that herbal medicines have no any side effects, also it is inexpensive and easily accessible. Besides, natural products have numerous active constituents. Hence, it is uncertain which compounds that have pharmacology activity. However, their multi-compounds are able to create synergistic reaction and increase the interactions[7]. In rationalizing the development of diabetes drugs, it is hoped that the synergy effect of a combination of two diabetes potential herbs.

People who use herbal medicines and nutritional supplements report their primary source of Note only from their friends or relatives in 80% of cases[8]. 44.7% never reported herbal usage to their physician, and 11% did so only rarely[9]. Worse still, in one survey 51% of doctors believed that herbal medicines have no or only mild adverse effects and 75% admitted that they had little or no knowledge about herb[10]. Many pharmacists (like many doctors) do not feel that they have enough basic knowledge themselves, or Note readily available, to recommend these safely, although, according to a study in an international cohort of pharmacists, 84% have tried CAM (complementary and alternative medicine) at some time in their life, and 81% still felt that they

Cite this article: Fadhilah Z, Elya B, Setiawan H, Nugroho GA, Masaenah FEW, Arianti V. Antidiabetic Activity and Phytochemical Constituents of *Syzygium cumini Leave* in Kadipaten, Central Java Indonesia, Indonesia. Pharmacogn J. 2021;13(6): 1502-1508.

had inadequate skills and knowledge to counsel patients[11]. Jamblang (*Syzigium cumini*) are common use as antidiabetic herb (as etnomedical use). This study aims to evaluate the effectiveness and the safety of the jamblang leaf extract as an antidiabetic.

MATERIAL

Plant material

Sample used in this study was the leaf of *Syzigium cumini* (Jamblang which was obtained from Kadipaten, Central Java Indonesia.

Animals Preparation

The test animal that used is the male Sprague Dawley white rat for antiabetic test. Which is obtained from the Biopharmaca Research Center (Biopharmaca), IPB University, Indonesia. The animal test research protocol whis is used in the research was accepted from Health Research Ethics Commission, Faculty of Medicine, University of Indonesia, and has obtained an ethical license with the number KET-807 / UN2.F1 / ETIK / PPM.00.02 / 2019 with protocol number 19-07 -0853. The ages of rats are 8-12 weeks. Their body weight about 180-200 grams. The animals were maintained at 22–24°C, with 75% relative humidity with light and dark periods at 12-h light/12-h dark intervals, starting at 6 a.m. Animals had free access to food and water (*adlibitung*), and were acclimatized for one week before the beginning of the experiment.

Chemicals

Ketamine (Kepro-Holland), xylazine (Interchemie-Holland), 70% ethanol (Brataco Chemika, Indonesia), aquades (Brataco Chemika, Indonesia), toluene P (Brataco Chemika, Indnesia), chloroform P (Brataco Chemika, Indonesia), ammonia P (Brataco Chemika, Indonesia), acetone P (Brataco Chemika, Indonesia), formic acid P, acetonitrile PA (Merck-Germany), methanol PA (Merck-Germany), ether P (Brataco Chemika, Indonesia), glacial acetic acid P (Brataco Chemika, Indonesia), hydrochloric acid (Brataco Chemika, Indonesia), concentrated sulfuric acid (Brataco Chemika, Indonesia), sodium hydroxide (Brataco Chemika, Indonesia), iron (III) chloride (Brataco Chemika, Indonesia), sodium bicarbonate, sodium chloride (Merck-Germany), glucose (Brataco Chemika, Indonesia), 0.1 M citrate buffer (pH 4.5), 0.1 M tris-HCl buffer (pH 7.4) , Follin Ciocalteu reagent (Brataco Chemika, Indonesia), Mg powder (Brataco Chemika, Indonesia), Dragendorff reagent (Sigma-Aldrich), Mayer, Wagn er, Lieberman-Bouchard, 10% gelatin solution (Brataco Chemika, Indonesia), 60 F254 silica gel plate (Merck-Germany), andrografolid (Sigma-Aldrich), myricetin (Sigma-Aldrich), brazilim (Sigma-Aldrich), buffer nitro formalin (Sigma-Aldrich), streptozotocin (Wako-Japan), nicotinamide (Merck-Germany), Januvia® tablets (Merck Sharp & Dohme)

Strandaritation of Raw Material

A. Sample Preparation

The leaf of *Syzigium cumini* (Jamblang) which are obtained from Kadipaten, Central Java, were freshly picked, collected, sorted, dried, and then crushed until they became smaller.

B. Quality Control of Raw Material

Quality control is divided on two parameters, specific parameters and non-specific parameters. The specific parameters that will be carried out consist of organoleptic, macro-microscopic, water-soluble extract, and ethanol-soluble extract content. The non-specific parameter examination carried out in this study consisted of total ash content, acid insoluble ash content, and drying loss. Each parameter is carried out three times.

1. Organoleptic Test

Simplicia powder was described about the shape, color, smell and taste using the senses. Form texture such as solid, dry powder, viscous, liquid. Color criteria such as yellow, brown, red, and so on. Odor criteria such as aromatic, odorless, and so on. While the taste criteria are bitter, sweet, chelate and so on (Indonesia Ministry of Health, 2000).

2. Water-soluble Content Level

5 grams of extract powder be put into a clogged flask, 100 mL of chloroform P water is added, shaken repeatedly for the first 6 hours, and left for 18 hours. The results were filtered, then 20 mL of the filtrate was evaporated to dryness in a shallow. Flat-bottomed dish that had been heated to 105°C and been tared, and the rest was heated at 105°C until a fixed weight. Then the levels are calculated in% water-soluble extract (Ministry of Health, 2000).

The equation of Water-Soluble Content:

$$\left(\frac{\text{plate \& extract weight} - \text{plate weight}}{\text{extract weight}}\right) \text{x disolution factor } of\ water \text{ x } 100\%$$

3. Ethanol-soluble Content Level

The powder is weighed as much as 5 grams then put in a clogged flask, add 100 mL of 95% P ethanol, shake repeatedly for the first 6 hours, and leave for 18 hours. The results were filtered quickly to avoid the evaporation of ethanol, then 20 mL of the filtrate was evaporated to dryness in a shallow flat dish that had been heated to 105°C and be tared, until a fixed weight. Then calculate the levels in% water soluble (Ministry of Health, 2000).

The equation of Ethanol-Soluble Content:

$$\left(\frac{\text{plate \& extract weight} - \text{plate weight}}{\text{extract weight}}\right) \text{x disolution factor } of\ ethanol \text{ x } 100\%$$

4. Dry Residu

The bottle were prepared and heated at 105°C for 30 minutes, then weighed. The bottles were reheated at 105°C for 30 minutes, then weighed again until they reached a fixed weight. After that, the simplicia powder was weighed as much as one gram then heated at 105°C for 1 hour and weighed again. The drying process is continued and weighed again for 1 hour until the difference between consecutive weights is not more than the point which mentioned on Indonesian Herb Pharmacopoeia. This test can also be done using a mouisture ballance tool, by placing 3 grams of simplicia on a detector plate, then putting it in a moisture balance container, until the equilibrium point is reached and the drying loss rate is known (Indonesian Ministry of Health, 2000 with modification).

The equation of Dry Residu:

$$\left(\frac{\text{extract weight} - (\text{preliminely extract weight \& bottle} - \text{the end weight of exctract \& bottle})}{\text{extract weight}}\right) \text{x} 100\%$$

5. Total Ash Content

The simplicia powder was weighed approximately 2 grams, then put in a silicate crucible that had been incandescent and tared, then slowly stirred until the charcoal ran out, cooled and weighed. If the charcoal cannot be removed, hot water is added to the sample and filtered through an ash-free filter paper. Then, apply filter paper and the rest of the filtering in the same crucible. The filtrate is put into a crucible, evaporated and annealed until the weight remains. The total ash content is calculated against the weight of the test material expressed in% w / w (Indonesian Ministry of Health, 2000).

Figure 1. Simplicia Syzigii cuminii folium. Description: (A) Jamblang leaf dry simplicia, (B) Jamblang leaf simplicia powder.

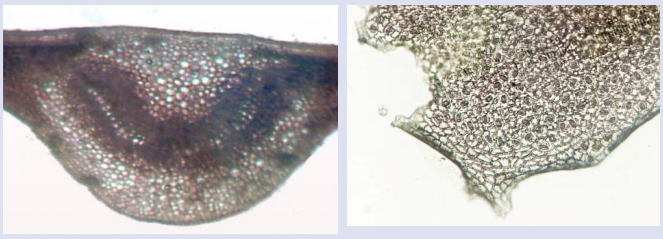

Figure 2. Microscopic Profile of leaves S. cumini (A) Transverse Incision of Leaf Bone Area (B) Longitudinal Incision of Leaf Adaxial Area, Magnification of 100X.

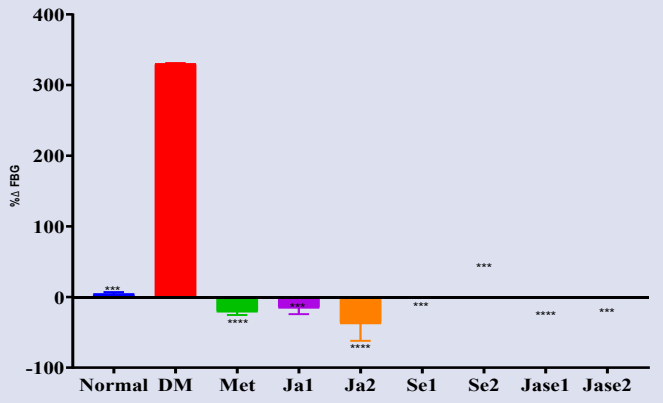

Figure 3. Changes in GDP after Therapy. Note: Normal (n = 4) p: 0.0003, DM (n = 4) p: <0.0001, Met (n = 4) p: <0.0001, Ja 1 (n = 4) p: <0.0001, Ja 2 (n = 4) p: <0.0001.

Extraction (Simply Ethanolic Maceration Method)

Five kilograms of leaf of *Syzigium cumini* (Jamblang) was extracted using maseration method. Ethanol maseration elected to extraction method because of low cost —often used in Indonesian herb industry— and effective solvent to polar solutions. Myricetin and brazilin which were detected in *Syzigium cumini* (Jamblang) is polar. Ethanol extract then was evaporated using a rotary evaporator to obtain a crude ethanol extract (EE). The crude extract was condensed by waterbath. It was stored under room temperature.

Phytochemical Screening with Chemical Reactions

This phytochemical screening aims to determine the content of compounds contained in extracts of Jamblang leaf and secang wood. Screening was carried out to determine the presence of phenol compounds, flavonoids, tannins, saponins, glycosides, terpenoids, and anthraquinones. The work procedures carried out are in accordance with what has been stated in the Indonesian Herbal Pharmacopoeia (FHI).

Effectifity Test (Teurapeutical Potential of *Syzigium cumini* and *Caesalpinia sappan* Combination Extract)

The rats are grouped into normal and diabetic rats. The group of normal rats (5 rats) are treated and handled normally without any induction (same as acclimatization treatments). Treatment of diabetes was carried out by giving a high-fat diet for 16 weeks. To induce pancreatic beta cell damage in rats, intraperitoneal injection of streptozotocin (STZ) (N-(methyl nitroso carbamoyl) alpha-D-glucosamine, Sigma, St.Louis, MO, USA) was administered at a low dose (35 mg / kg body weight) twice at week 8 and 12. Prior to diabetes induction, the rats were fasted for 18 hours. STZ solution was prepared fresh by dissolving STZ with 0.1 M citrate buffer (pH 4.5). Evaluation of the condition of diabetes is carried out by measuring the blood sugar, oral glucose tolerance, body weight, in the blood to determine the status of the tested animals having diabetes. After it is known that diabetes is positive by determining fasting blood sugar levels above 250 mg / dL, 5 rats are grouped as one group of a negative control group, positive control group which is treated use metformin and 2 groups (5 rats each group) are treated with oral therapy for 14 days. one group of rats are divided to 50mg/ Kg BW of Syzigium cumini leaf extract and 100mg/Kg BW of Syzigium cumini leaf extract.

Microscopic observations by light microscope and Quantitative Analysis use ImageJ Software

Microscopic analysis of the histopatologycal analyze was performed using a light microscope which equipped with microcam tool. Quantitative analysis use ImageJ Cell Counting Software and assased by Primate Research Center (the animal laboratory which have been International Certified of ISO9001 accreditation), IPB University, Bogor City West Java, Indonesia.

Statistical analysis

All the experimental data results are expressed as mean ± SEM. Analyzes were performed using GraphPad Prism 8.0.2 software version. Which are detected as parametric and non-parametric date by normality distribution test (Kolmogorov Smirnov and Shapiro Wilk Test) and homogeneity distribution use Fisherman Test. After divided into parametric and non-parametric category, parametric date is analyzed by two-way ANOVA and non-parametric test is analyzed by Kruskal-Wallis Test, then Post Hock Test use Original FDR method of Benjamini and Hochberg.

RESULTS AND DISCUSSIONS

Standardization of Extract Quality

Simplicia Determination

a. Organoleptic Test

The leaves of Jamblang (*S. cumini*) appear to be brownish in color, have a distinctive aroma, and are not bitter in taste (Table 1).

b. Morphological Evaluation (Macroscopic)

Syzygium cumini

Based on the observation, the leave of *Syzigium cumini* has morphological characteristics 7-18 cm long and wide 3-8 cm. The

Table 1: Crude Simplicia Organoleptic Test.

Organoleptic Characteristic	RResult
Shape	Crude dry
Odor	Aromatical
Color	Green brownish
Flavor	No taste

Table 2: Non-Specific Parameter of Extracts Test.

Characteristics of Extract	Method	Syzygium cumini	Limit
Extract Yield (%)	maceration	22.55	-
Total Ash Contain (%)	Gravimetry	0.30	<10
Moisture (%)	Gravimetry	8.3	<10
Levels Water Soluble Extract (%)	Gravimetry	22.95	> 15
Ethanol Soluble Extract (%)	Gravimetry	32.24	> 9
Pb (ppm)	AAS	8.00	<10
Cd (ppm)	AAS	-	< 0.3

Table 3: Phytochemical Parameters Phytochemical.

Parameters	Syzygium cumini
Alkaloid	+
Saponins	+
Triterpenoids	+
Tannins	+
Phenolic Content	+
Flavonoids	+
Steroids	+
Glycosides	+

Table 4: Comparison of Body Weight During Induction Period.

Group	Weight (g)		
	Before STZ-1	After STZ-1	After STZ-2
Normal (n = 5)	197.0 ± 8.14	200.8 ± 8.25	208.6 ± 8.68
DM (n = 5)	188.4 ± 7.53	185.4 ± 6.68	190.8 ± 7.83
Met (n = 5)	173.2 ± 6.52	178.0 ± 6.19	157.9 ± 19.28
Ja1 (n = 5)	189.2 ± 11.75	180.6 ± 3,763	176.6 ± 4.48
Ja2 (n = 5)	187.4 ± 5.98	184.6 ± 3.36	184.6 ± 6.14

The results presented are Mean ± SEM.

leaves are oblongatus-ovatus, apex tapered (akuminatus). The base of the leaves is cuneate or round; short, round, or blunt crest; edges narrow towards the petiole and the edges of the leaves are slightly wavy. Has smooth leaf venation, close together, parallel, and dotted glands. Based on these morphological characteristics, the simplicia leaves have the characteristics of the species *Syzygium cumini*.

c. Anatomical Evaluation (Microscopic)

Syzygium cumini

Anatomically (microscopically) transversally observed epidermal tissue in top surface (abaxial) and lower surface (adaxial) of the leaf, followed by leaf parenchyma tissue (mesophyll cylindrical at the abaxial and spongy mesophyll below). In the middle there is a vascular bundle of closed collateral type (typical of dicot plants). In the tangential / longitudinal incision in the adaxial part of the leaf, a number of parenchyma cells and parasitic stomata (guard cells surround the lip of the stomata, without accompanying cells) are seen.

Characterization of Extract

Organoleptic observations on the liquid extract of Jamblang leaves (*Syzigium cuminii), it* appears that the liquid extract of the Jamblang leaves looks slightly brownish. When the aroma is smelled the leaf extract has a distinctive aroma. In the secang wood extract, in contrast to the dry powder which is reddish orange in color, the liquid extract looks a bit dark orange to orange and has no aroma.

Non-Specific-specific

Non-specific Parameters evaluation of the extracts determined in this study included moisture content, ash content, acid insoluble ash content, heavy metal contaminants, microbiological contaminants and residual ethanol solvent. The purpose of this examination is to ensure the quality of the extracts used in research so as to guarantee its safety. The extraction of 1.5 kg of Jamblang leaf simplicia yielded 243.2 gr of 70% ethanol extract, the yield obtained was 22.55%.

Based on the results of the non-specific parameter test of the quality analysis of Jamblang has qualified of extract standard required by the Indonesian Herbal Pharmacopoeia. Extracts that have good quality will certainly affect performance and effectiveness in providing optimal properties.

Specific Parameters Specific

Parameters determined in this study include phytochemical screening and determination of chemical content.

Phytochemical Screening

In this study, phytochemical screening was carried out on the extract of Jamblang leaves. Phytochemical screening is carried out on critical parameters which are the eligibility requirements for extracts as raw material for traditional medicinal preparations. The results of phytochemical screening and biomarker levels in each extract are presented in Table 3.

Antidiabetic Activity Test

Diabetes Animal Model Manufacturing

Pathophysiology of type 2 diabetes mellitus occurs as a result of a long-lasting combination of several aspects. In making animal models, it is expected that the induction given can accelerate the symptoms of diabetes, without the need for a long time. Diabetes induction, which is carried out to form animal models, can be done in several ways, including using chemical agents[12], pancreatic surgery[13], genetic induction, and induction using viruses[14]. In this research, induction using a chemical agent, namely STZ, is used as a diabetogenic agent. In addition to chemical induction using STZ, which indirectly causes alkylation in the DNA of β cells. The aspects of diabetes symptoms that are targeted are decreased insulin secretion, insulin resistance, and the ominous octet as is common in type 2 diabetes mellitus or diabetes that is formed due to lifestyle errors[14].

The decrease in insulin secretion was induced by giving a low dose of STZ injection (35mg / Kg BW) intraperitonially as a diabetogenic agent. An indicator of the success of this decrease in insulin secretion is characterized by high levels of sugar in the blood, as a manifestation of reduced insulin which supports glucose uptake to peripheral tissues. STZ is used as a diabetogenic agent that causes selective damage to β cells, resulting in insulin deficiency, hyperglycemia, polydipsia and polyuria that resemble diabetes in humans. The specific mechanism of STZ is as a diabetogenic agent through DNA alkylation. Animal models with STZ induction are often used as animal models to assess the pathological consequences of diabetes and screening therapy according to these pathological conditions[15].

Insulin resistance will occur when the nutrient storage channel in charge of maximizing energy use efficiency is exposed continuously to a surplus of energy. This energy surplus will reduce insulin sensitivity. This scenario is induced by using the High Fat Diet (HFD) with a fat composition of 24.99%, 15.85% protein and 3.16% organic fiber (crude). Animal feed is categorized as HFD if the fat content is 15% more than normal feed in[16]. It is hoped that the provision of HFD will have an impact on obesity in test animals. The condition of obesity is characterized by an excess body weight of 15-20% compared to the normal optimum ideal weight in animals. The type of obesity aimed at this study is metabolic obesity (due to an imbalance in the metabolism of carbohydrates and fats in the body.

The HFD feeding scheme is also supported by a higher quantity and portion of feed compared to control mice given normal diet. body weight that exceeds 15% of ideal weight, symptoms of obesity are also characterized by high production of cholesterol and triglycerides in the liver, while low HDL levels[17]. This study used an animal model of Sprague Dawley (SD) rats. A total of 40 male SD rats induced with high-fat and low-dose STZ feed. STZ injection was carried out twice 1 week after the first injection. Fasting blood glucose and lipid profile checks were monitored after STZ administration to determine the diabetic model animal for the study. fasting blood is done by drawing blood through the eco r with a glucometer check.

In the observations during the period before and after giving induction to body weight in the test group. Even *High Fat Diet* though was given, it did not provide a significant change in body weight, but when viewed from the lipid profile, there were significant differences in animal models, before and after induction.

Main Test: Antidiabetic Testing

Changes in GDP

Based on the anti-hyperglycemic activity test, the results showed a decrease in fasting blood sugar compared to diabetic mice. In the normal group, fasting blood sugar tended to be stable, while the diabetic rats continued to experience an increase in fasting blood sugar. The difference in GDP in the normal group is very significant with a value of p = 0.0003. On the administration of metformin oral administration, there was a very significant decrease in GDP with p value <0.0001, so that it can be stated that the positive control in this study worked well, metformin as a standard drug worked as it should. Metformin is generally used in the basic algorithm for managing diabetes management, especially in type 2 diabetes[18].

In giving a single extract the best reduction in GDP in this study was shown by Jamblang 2 (giving Jamblang at a dose of 100 mg / Kg BW). In the oral administration of single extract p value in the Jamblang 1 group (giving Jamblang extract at a dose of 50 mg / Kg BW), Jamblang 2 (giving Jamblang at a dose of 100 mg / Kg BW). To find out what mechanism happened to cause a decline in GDP, further research is needed.

DISSCUSSION

Based on its effectiveness as an anti-hyperglycemia, oral administration of Jamblang has a significant effect on reducing fasting blood glucose levels in rat, when compared to negative controls (DM group). If based on the chemical constituents contained in both Jamblang leaf extract, such as alkaloids, saponins, tannins, phenols, flavonoids, steroids, and also glycosides, there are several mechanisms that may be involved in the process of reducing GDP. Based on the research that has been done, these constituents have the potential for antidiabetic activity. Alkaloid compounds function to facilitate glucose uptake, increase insulin secretion and help regenerate pancreatic β-cells[19]. Flavonoid compounds that act as *insulinomatic*, increase insulin secretion, play a role in glucose-lipid metabolism by activating PPAR, and increasing glycolysis[20]. Saponin compounds as stimulants in regenerating pancreatic β-cells and play a role in increasing insulin secretion[21]. Phenolic compounds and their derivatives facilitate the digestion of carbohydrates, increase insulin secretion, and inhibit α-Glucosidase[22]. Tannins are known to stimulate β-pancreatic cell regeneration[23]. Glycoside compounds can stimulate the synthesis of glycogen as muscle sugar stores, facilitate absorption of carbohydrates, and help increase insulin secretion, some glycosides are known to stimulate β-pancreatic cell regeneration to β-pancreatic cell regeneration[24]. The mechanism that occurs in the phenomenon of the decline in GDP in this study cannot be completely ascertained.

CONCLUSION

Oral administration of Jamblang has a significant effect on reducing fasting blood glucose levels in rat, when compared to negative controls (DM group). However, the mechanism that occurs in the phenomenon of the decline in GDP in this study need further study.

ACKNOWLEDGEMENT

We would like to acknowledge the financial assistance obtained from the "Grant PUTI (Scopus Indexed Publication Scholarship) University of Indonesia (Number: r: BA-1518/UN2.RST/PPM.00.03.01/2020) and Mark Herb, School of Pharmacy ITB for supporting standart solution for this research.

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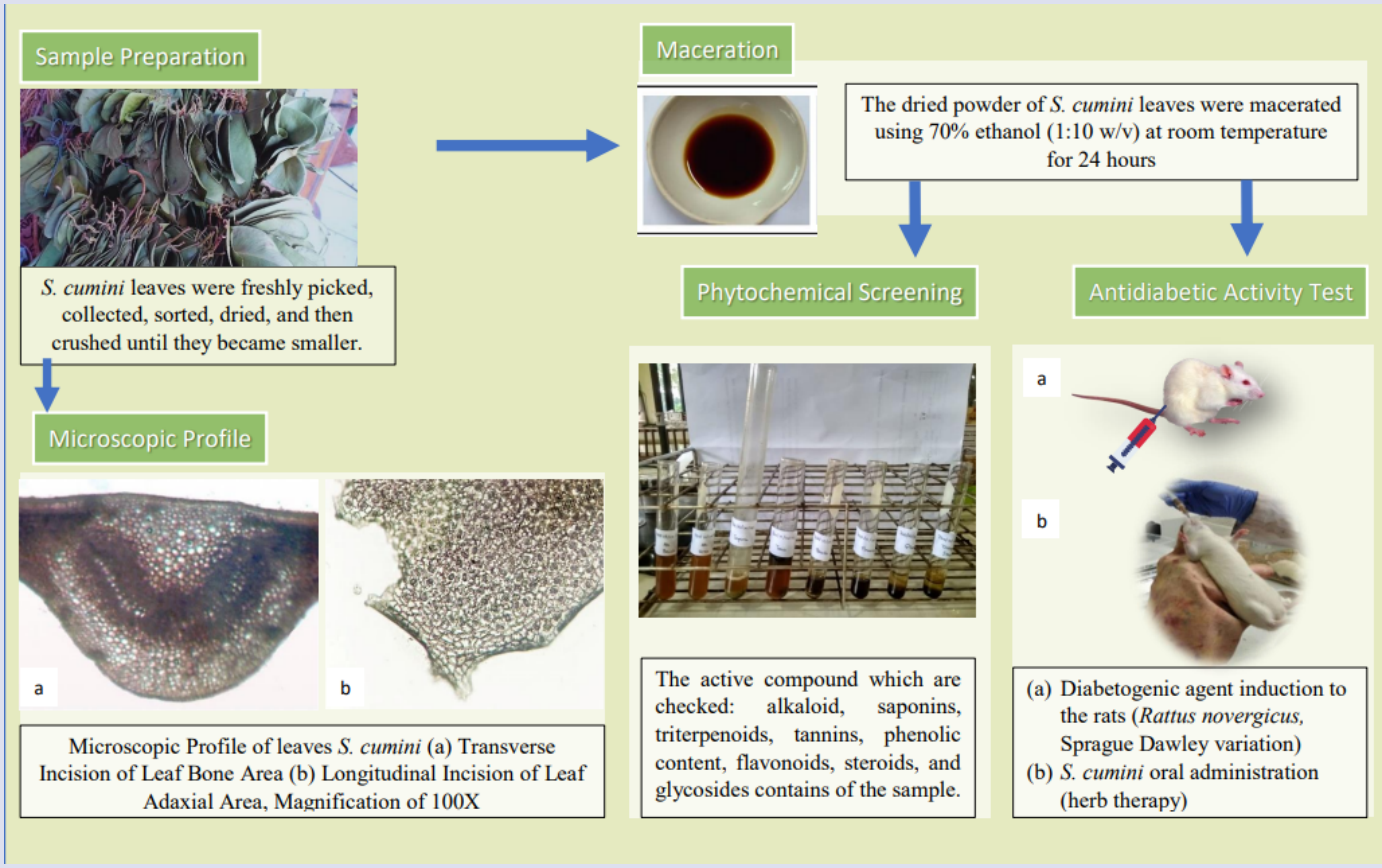
GRAPHICAL ABSTRACT



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Cite this article: Fadhilah Z, Elya B, Setiawan H, Nugroho GA, Masaenah FEW, Arianti V. Antidiabetic Activity and Phytochemical Constituents of *Syzygium cumini Leave* in Kadipaten, Central Java Indonesia, Indonesia. Pharmacogn J. 2021;13(6): 1502-1508.