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INTRODUCTION Diabetes (or diabetes mellitus; DM) is a chronic metabolic disease characterized by increased blood glucose levels1. These conditions are associated with carbohydrate, fat, and protein metabolism disorders due to insulin and severe conditions of microvascular, macrovascular, and chronic neuropathy2. Approximately 476 million people worldwide have DM, mostly in poor and developing countries3. The prevalence of DM in Indonesia is 6.2%, and Indonesia is among the ten countries with 10 million living with DM4.

The American Diabetes Association classifies DM into 4; DM type 1, type 2, gestational DM, and certain types of DM due to other causes such as monogenic diabetes syndrome, exocrine pancreatic disease, and DM trigger drugs1,5. In the last three decades, the prevalence of type 2 diabetes (T2DM) has increased dramatically. Affordability of access to treatment, including insulin, is essential for the survival of people with DM6,7. However, therapy for T2DM uses more antihyperglycemic drugs rather than insulin, such as biguanides, sulfonylureas, meglitinides, thiazolidinedione (TZD), dipeptidyl peptidase 4 (DPP-4) inhibitors, sodium-glucose cotransporter inhibitors (SGLT2), and a-glucosidase inhibitors, which is synthetic drugs with various adverse effects8. Diabetes mellitus treatment without adverse effects is still the biggest challenge for medical practitioners.

Synthetic drugs used to treat DM are often associated with various disturbing adverse effects such as nausea, vomiting, dysentery, alcohol flush, migraines, swelling, malignant anemia, and fainting9,10. For this reason, the approach currently being developed by many researchers is to develop natural herbal preparations as DM therapy11. Traditional medicine is carried out from generation to generation because it is believed to be an effective treatment with minimal side effects. However, most of the plants used have not been scientifically tested.

The increase in traditional medicines is the reason for the many studies related to the efficacy of secondary metabolites found in plants12,13. According to world ethnobotanical, 800 medicinal plants are used for the prevention of T2DM. Clinically proven that only 450 medicinal plants possess anti-diabetic properties, from which 109 medicinal plants have a complete mechanism of action14. One of the medicinal plants interesting to research regarding its properties as an antihyperglycemic is bawang dayak, a typical plant from Central Kalimantan, Indonesia.

Bawang dayak or Eleutherine palmifolia is believed to have the efficacy of curing various types of diseases, including DM15. Secondary metabolites of bawang dayak bulbs contain alkaloids, saponins, tannins, phenolics, triterpenoids, steroids, sterols, and flavonoids16,17. Bawang dayak bulbs have activity as an inhibitor of a-glucosidase,

assisting lower glucose levels in the body18.

The a-glucosidase inhibitors are one of the antidiabetic agents that work by inhibiting a-glucosidase, in which this enzyme plays a role in the decomposition of polysaccharides into monosaccharides19. Research on the effects of bawang dayak has been widely reported, both related to chemical compound content and various pharmacological activities of bawang dayak, including reducing blood glucose levels. However, previous studies on the effects of bawang dayak only compared the activity between bawang dayak extract and oral diabetes drugs; There has been no research on the effects of bawang dayak extract combined with oral diabetes drugs.

One of them is the research results of Febrinda et al.15, which showed that 100 mg/kg of bawang dayak extract could maintain the bodyweight of diabetic rats and significantly reduce blood serum glucose levels. The difference between this study and the previous study was in the treatment, where the test animals were given a combination of bawang dayak extract and the oral diabetes drug: acarbose. The choice of acarbose is based on its mechanism of action, which works as a-glucosidase inhibitors so that it is expected to provide a synergistic effect with bawang dayak extract20.

The purpose of this study was to compare the hypoglycemic effect between the combination of bawang dayak extract and acarbose with single acarbose. MATERIALS AND METHODS Materials The test subject was a white rat, Strain Sprague-Dawley, aged two to three months and weighing 200-250 g. The ingredients used were bawang dayak bulbs, 96% ethanol, acarbose, and dexamethasone injection. Fresh bawang dayak bulbs (Figure 1) were collected from Palangka Raya, Central Kalimantan, Indonesia.

Plant determination was carried out by the Basic Laboratory of the Faculty of Mathematics and Science, Universitas Lambung Mangkurat, and identified as Eleutherine palmifolia (L) Merr. The instruments used were rotary evaporators, water baths, injection syringes, animal scales, glucose strips, and digital glucometers. / Figure 1. Fresh bawang dayak bulbs Methods Preparation of simplicia powder Fresh bawang dayak bulbs cleaned of dirt and then washed with running water until clean. The bulbs were then cut and oven-dried at 40°C.

The purpose of producing simplicia into powder was to increase the surface area of ??the bulbs so that the surface of simplicia in contact with the solvent becomes broader, and more active compounds could be extracted21. The resulting powder was then sieved with mesh number 20. Preparation of ethanol extract Bawang dayak powder was put into the maceration chamber and then extracted with 96% ethanol solvent with a sample : solvent ratio of 1 : 1. The maceration process was carried out for three days

with solvent replacement every 24 hours, alternated with stirring every 6 hours. The liquid extract obtained was then collected and concentrated using a rotary evaporator at 40-50°C.

The thick extract obtained was then dried using a water bath at a temperature of 50°C until a constant weight was obtained. Preparation of test animals The test animals used were white Sprague-Dawley rats aged two to three months, with a bodyweight of 200-250 g obtained from CV. Mera Medika. The test animals were placed in cages at room temperature with a light/dark cycle every 12 hours and fed with standard animal pellets and free water.

This research was conducted following established ethical norms and approved by the Medical Research Ethics Committee of the Faculty of Medicine, Universitas Lambung Mangkurat (No. 407/KEPK-FK UNLAM/EC/IX/2020). All test animals were then fasted for 12 hours before the experiment but were given free access to water. Blood glucose level reduction test All test animals had their blood glucose levels measured to determine their blood glucose levels before treatment. All test animals were then divided into two groups, each consisting of 16 test animals. Each group was then injected with dexamethasone at a 1 mg/kg BW dose dissolved in 0.9% NaCl subcutaneously22.

On the 13th day after giving dexamethasone, blood glucose levels were measured using glucose strips and digital glucometers. Each group of test animals was then subjected to an antihyperglycemic test. The dose of bawang dayak extract used in this study was 100 mg/kg BW and acarbose 40 mg/100 g BW. The first group was treated with a combination of bawang dayak bulbs and acarbose for 15 days, and the second group was treated with acarbose only for 15 days.

Fasting blood glucose measurements of test animals were carried out from the tail blood vessels (lateral veins). Data collection was carried out every three days for 15 days after being fulfilled for +10 hours with measurements using glucose strips and digital glucometers. Data analysis For data analysis, the parameter used was a decrease in fasting blood glucose levels. The decrease in fasting blood glucose levels in the control and test groups was analyzed by using the General Linear Model test at a 95% confidence level.

RESULTS AND DISCUSSION Extraction was carried out by maceration of 2 kg of bawang dayak bulbs using 96% ethanol as a solvent. The dry extract obtained was 46 g, so the yield of the extract obtained was 2.3%. This number is smaller than other studies, as reported by Yuswi23 with a yield of 7.58% and Novaryatiin et al.24 with 6.65%. This difference was mainly influenced by the extraction method used, in which the

maceration method does give lower yields than reflux or percolation. However, the maceration procedure was relatively easy because it did not require continuous attention21.

Figure 2 shows the average blood glucose levels from D+3 to D+15 in the combination group of bawang dayak and acarbose as well as the single acarbose group. From Figure 2, it can be seen that the average glucose level in the combination group was lower than that in the single acarbose group. The General Linear Model test results obtained a p-value of 0.00, which means that there is a significant difference in the decrease in blood glucose levels of the test animals. / Figure 2.

Blood glucose level of each test group during observation In this study, it was found that after administering subcutaneous dexamethasone to mice for 12 days, there was an increase in blood glucose levels exceeding normal blood glucose levels in mice (50-135 mg/dL)25. Dexamethasone administration would increase blood glucose levels and reduce insulin sensitivity26. Studies with rodent models show that glucocorticoids regulate lipid metabolism in skeletal muscle by increasing ß-oxidation and lipolysis27. In addition, administration of glucocorticoids also results in inhibition of 11ß-HSD1 expressed in muscle, thereby decreasing lipogenic and lipolytic genes28.

Therefore, glucocorticoids regulate carbohydrate and lipid metabolism in skeletal muscle, which could play an essential role in regulating muscle insulin sensitivity throughout the body29. The results showed a decrease in blood glucose levels in the test animals in both groups. However, the combination group's decrease in blood glucose levels was lower than the single acarbose group, with the most significant difference occurring on day 9 with 21.69 mg/dL.

After that, the difference between the two groups decreased until the 15th day; the difference was 10.38 mg/dL. These results indicate that the optimal effect of the bawang dayak extract and acarbose combination was shown on the 9th day after administration. The decrease in blood glucose levels in the combination group of bawang dayak and acarbose on day 12 was within the range of normal blood glucose levels in test animals. The results indicate that the active compounds in bawang dayak provide a synergistic effect with acarbose to reduce blood glucose levels.

These results are in line with previous studies that reported that bawang dayak extract showed a significant ability to lower blood glucose levels than untreated test animals; besides can also increase the concentration of insulin15,30,31. Bawang dayak contains several phytochemical compounds such as flavonoids, alkaloids, tannins, and saponins, each of which has an anti-diabetic role. The flavonoid compound group is reported to

have anti-diabetic activity by regenerating damaged pancreatic ß-cells32.

Alkaloids and <mark>tannins have astringent properties</mark> by inhibiting the absorption of sugar on the surface of the small intestine, which in turn can lower blood sugar levels33. Whereas saponins can regenerate pancreatic cells, causing an increase in the number of pancreatic ß-cells and islets of Langerhans increases insulin secretion. Increased insulin secretion will help lower blood sugar levels34. CONCLUSION The combination of bawang dayak extract and acarbose can <mark>reduce blood glucose levels to</mark> a greater extent than single acarbose.

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