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# The Effect of Propolis *Trigona* sp. Water Extract from North Lombok on Blood Sugar Levels in Vivo

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**Abstract:** Propolis has been touted for its ability to regulate blood sugar levels in diabetes, but the effectiveness can vary depending on the region. A study was conducted to investigate the effect of propolis *Trigona* sp. water extract on blood sugar levels in vivo. The mice were divided into three groups, with four mice in each group. The positive control group received a 5 mg/kgBW glibenclamide suspension, the negative control group was given a 0.25% CMC-Na suspension, and the treatment group was administered with water extract of propolis at a dose of 300 mg/kgBW. All groups were induced with a 20% D-glucose solution intraperitoneally, and blood sugar levels were measured at 15, 30, 60, 90, and 120 minutes via the tail vein. The blood sugar data was analyzed and presented descriptively. The Mann-Whitney statistical analysis was used to determine the results, revealing that the water extract of propolis at 300 mg/kgBW did not have a significant effect on reducing blood sugar levels in animals induced by a 20% D-glucose solution, with a significance value ($p < 0.05$).

**Keywords:** Hypoglycemic test; In vivo; OGTT; Propolis; *Trigona sp.*

## Introduction

Diabetes mellitus (DM) is a disease characterized by blood glucose (blood sugar) levels that are higher than usual (Wahyu, 2017). Diabetes mellitus is a metabolic disorder associated with hyperglycemia due to abnormalities in insulin secretion, insulin action, or both (Sapra et al., 2023). Diabetes mellitus is classified into four kinds: type 1 DM, type 2 DM, gestational DM, and various types of DM (Soelistijo et al., 2021). Based on Indonesian Basic Health Research data from 2013, the prevalence of diabetes mellitus in Indonesian society was 1.5%, although it climbed to 2.0% in 2018. Diabetes mellitus prevalence increased in the NTB region in 2013, rising from 0.9% to 1.2% in 2018.

Synthetic antidiabetics can be used to treat diabetes mellitus, but long-term use entails the danger of triggering negative effects, thus natural substances are chosen as an option for treating diabetes (Soelistijo et al., 2021; Suliska et al., 2020). Propolis is a natural substance that is utilized as an alternative treatment for diabetes (Shafriani, 2021).

Propolis is a sticky, resin-like substance gathered by honey bees. Propolis contains secretions or exudates originating from many sections of plants, including rabbits, shoots, and leaves, as well as tree exudates (Hasan et al., 2013; Nagai et al., 2003; Rismawati et al., 2017). Propolis contains secondary metabolite chemicals such as alkaloids, flavonoids, tannins, and saponins (Zahra et al., 2021). According to Wang et al. (2004), an ethanol extract of propolis evaluated on alloxan-induced diabetic rabbits affected lowering blood glucose levels. Then, in Murata et al. (2004) study, propolis was found to have an antihyperglycemic effect in patients with type

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2 diabetes mellitus. According to Fuliang et al. (2005), propolis ethanol extract and water extract affected lowering of blood sugar. Levels and modifying glucose metabolism as well as blood lipids, which will reduce lipid peroxidation and free radical formation in diabetic mice. El-Sayed et al. (2009) discovered that an ethanol extract of propolis had anti-diabetic and hypolipidemic effects, which contributed to its antioxidant capacity in pancreatic tissue in streptozotocin-induced diabetic rats at a dose of 60 mg/kg intraperitoneally for three days.

Previously, research had been carried out on Trigona sp propolis from North Lombok by Zahra et al. (2021) regarding its physicochemical characteristics, but in vivo testing has not been carried out. Physicochemical characteristics can provide an overview regarding the content of secondary metabolite compounds that play a role in biological activity, especially as antihyperglycemic which is currently the disease with the third highest prevalence of 11.3% in 2020 with a death toll reaching 236,711 people (International Diabetes Federation, 2021; Kemenkes RI, 2020).

The aim of this study was to investigate the effect of *Trigona* sp. propolis water extract from North Lombok on blood glucose levels in vivo.

## Method

*Research Design*

This study is experimental research. The effect of Propolis *Trigona* sp. water extract from North Lombok on Blood Sugar Levels in Vivo.

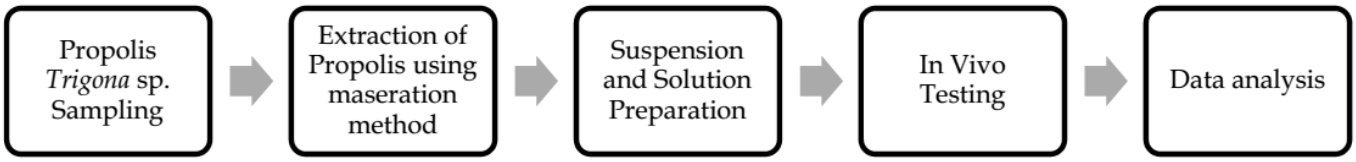


**Figure 1.** Research procedure

*Materials and Tools*

Materials and equipment that are required for the test are alcohol, aqua destillata, 0.9% NaCl infusion fluid, CMC-Na, D-glucose, 70% ethanol, 5 mg glibenclamide, glucose touch strip test, propolis water extract sample, laboratory glassware, sterile falcon tube, glucometer, surgical scissors, 25G needle, mouse cage, 0.2 um filter membrane, micro water bath, mouse restrainer, mouse oral probe, syringe, analytical balance, and vial.

*Sampling*

Propolis samples were obtained from the Faculty of Food Technology and Agroindustry, University of Mataram. The obtained propolis is unprocessed propolis.

*Extraction Method*

The extraction of propolis from *Trigona sp*. is achieved through the maceration method, which employs a water-based solvent. The initial step is to cut 200 grams of raw propolis into small pieces and dissolve them in 200 mL of water (in a ratio of 1:1, w/v) at a temperature of 45°C for three days. Throughout this process, the mixture is continuously stirred using a microwater bath. The resulting filtrate is obtained by decanting the mixture.

*CMC-Na 0.25% Suspension Preparation*

To prepare CMC-Na 0.25% Suspension, slowly add 0.05 grams of CMC-Na to 20 mL of boiling water in a mortar. Keep stirring until all parts of the CMC-Na are wetted. Then, crush the mixture until it is uniform, and transfer it to a vial.

*Propolis Water Extract Solution 300 mg/kgBW Preparation*

To prepare Propolis water extract solution 300 mg/kgBW, a liquid extract of propolis that has been filtered with Whatmann filter paper is put into a vial. A certain volume of the filtrate is taken into a volumetric flask, and distilled water is added up to the mark. The solution was shaken until homogeneous.

*Glibenclamide 5 mg/kgBW Suspension Preparation*

To prepare glibenclamide 5 mg/kgBW Suspension, a 5 mg glibenclamide tablet powder was added to the CMC-Na, which had been developed and crushed until homogeneous. Glibenclamide suspension is put into a vial.

*20% D-Glucose Solution Preparation*

To make a 20% D-glucose solution, it's crucial to follow aseptic techniques using the Flamer method. The work table should be cleaned with 70% alcohol before starting the process. Start by dissolving 2 g of D-glucose in 10 mL of a 0.9% NaCl infusion solution. Next, filter the solution through a 0.2 µm filter membrane into a sterilized 15-mL falcon tube. This process should be done carefully, following the guidelines provided by Benedé-Ubieto et al. (2020).

*In Vivo Testing*

In the hypoglycemic effect test with 20% D-Glucose Induction, 12 female Swiss Webster strain mice with weights ranging from 20 to 30 g were used, which were grouped into three groups, including positive control group glibenclamide 5 mg/kgBW, negative control group CMC-Na 0.25%, treatment group water extract propolis 300 mg/kgBW.

Prior to being induced with a 20% D-glucose solution, all the mice were fasted for 12 hours while still having access to drinking water. Blood sugar levels were measured using an Easytouch glucometer. Blood was drawn from the tip of the mouse's tail, which was cut into small pieces, and the blood was then dropped onto a glucose test strip. Fasting blood sugar levels (T0) were measured once the mice had finished fasting, and after that, the mice were administered a 20% D-glucose solution intraperitoneally. Blood sugar levels were then measured again at 15- and 30-minute intervals (Rahayuningsih et al., 2022).

At the 30-minute mark, each control group was administered the test suspension orally. The positive control group was given glibenclamide suspension, the negative control group was given CMC-Na suspension, and the treatment group was given propolis solution. Following this, blood sugar levels were measured at 60, 90, and 120 minutes.

The blood sugar levels obtained were then processed using SPSS 25 software, which includes homogeneity, Kolmogorov-Smirnov and Shapiro-Wilk normality tests, one-way ANOVA with post-hoc LSD, and Mann-Whitney with a confidence level of 0.05. All testing protocols using experimental animals have received approval from Komisi Etik Penelitian Kesehatan Fakultas Kedokteran Universitas Mataram (No: 274/UN18.F8/ETIK/2023).

## Results and Discussion

*Results*

Table 1 shows the results of phytochemical screening on propolis water liquid extract. The screening revealed the presence of secondary metabolite compounds such as alkaloids, flavonoids, tannins, quinone and triterpenoids. However, no saponins were detected in the extract. This information outlines the results of the phytochemical screening analysis of the propolis water liquid extract.

**Table 1.** Results of Phytochemical Screening of *Trigona sp*. Propolis Water Extract

| Testing | Reagents | Interpretation |
|---|---|---|
| Alkaloids | Dragendorff | (+) |
| | Mayer | (+) |
| | Wagner | (+) |
| Tannin | $FeCl_3$ 5% | (+) |
| | Gelatin 10% | (+) |
| Triterpenoids | Salkowski | (+) |
| quinone | NaOH 0.1 N | (+) |
| Flavonoid | | (+) |
| Saponin | | (-) |

Information:
(+) = There is a compound being tested
(-) = There is no compound tested

**Table 2.** Blood Sugar Levels of Mice in Each Group

| Group | Average Blood Sugar Levels in Each Group ± SD | | | | | |
|---|---|---|---|---|---|---|
| | T0 (Basal) | T1 (15′) | T2 (30′) | T3 (60′) | T4 (90′) | T5 (120′) |
| Positive | 111 ± 2.915 | 197 ± 26.532 | 132 ± 6.892 | 104 ± 8.573 | 93.5 ± 14.790 | 88.75 ± 9.807 |
| Negative | 113.5 ± 5.894 | 220.75 ± 36.663 | 187.5 ± 59.634 | 162 ± 33.369 | 121.75 ± 8.166 | 116 ± 4.5277 |
| Treatment | 108 ± 6.964 | 221.25 ± 33.055 | 186.5 ± 26.424 | 129 ± 14.404 | 116.5 ± 15.596 | 144.04 ± 13.964 |

Information: T0= Fasting blood sugar level before 20% D-glucose induction; T1= Blood sugar level 15 minutes after being induced by 20% D-glucose; T2= Blood sugar level at 30 minutes after therapy administration; T3= Blood sugar levels at 60 minutes and 30 minutes after therapy; T4= Blood sugar levels at 90 minutes and 60 minutes after therapy; T5= Blood sugar levels at 120 minutes and 90 minutes after therapy.

The decrease in blood sugar levels in mice induced by 20% D-glucose after administration of propolis liquid water extract can be seen in Table 2. The data presented in Table 2 indicates that prior to glucose induction, the blood sugar levels in the mice were less than 120 mg/dL. Glucose induction was carried out immediately after measuring the basal blood sugar levels. The blood sugar levels increased at the 15th minute following glucose induction but decreased at the 30th minute. At the 30th minute, all groups were induced with each test suspension or solution. From the 60$^{th}$ minute to the 120$^{th}$ minute, the blood sugar levels decreased, except for the test control group, which showed an increase in blood sugar levels at the 120$^{th}$ minute.

A graph showing the decrease in blood sugar levels in mice for each control can be found in Figure 2. As shown in Figure 2, the blood sugar levels of mice in all groups were measured and compared. The results indicated that the control treatment group had lower blood sugar levels compared to the negative control group. However, the blood sugar levels of mice in the

control treatment group were higher than those in the positive control group.

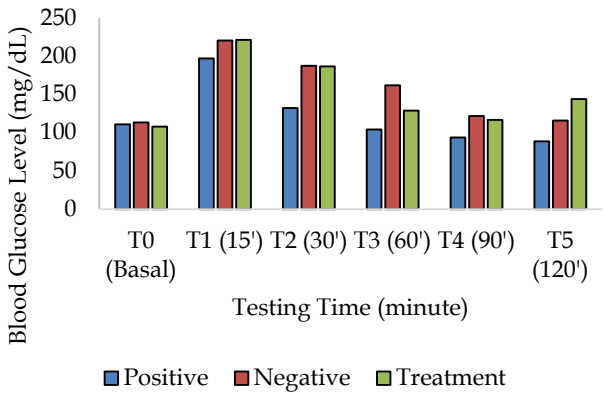


**Figure 2.** Graph showing the decrease in blood sugar levels of mice in all control groups

The normality and homogeneity of data on blood sugar levels of mice in each control are presented in Table 3.

**Table 3.** Homogeneity and Normality Test of Mice Blood Sugar Levels

| Test | Animal Groups | Kolmogorov -Smirnov Sig. | Shapiro-Wilk Sig. | Interpretation |
|---|---|---|---|---|
| Normality | Positive | 0.200 | 0.076 | Normal |
| | Negative | 0.200 | 0.259 | Normal |
| | Treatment | 0.200 | 0.378 | Normal |
| Homogeneity | | | 0.015 | Distributed homogenies |

Table 3 presents the results of two tests to check the normality and homogeneity of the blood sugar level data obtained during testing, as well as the distribution of data from each group. The obtained blood sugar level data was found to be normally distributed and homogenous, with a significance value of $p > 0.05$.

**Table 4.** One-Way Anova Test

| Test | Sig. | Interpretation |
|---|---|---|
| One-Way Anova Test | 0.466 | H0 Accepted |

The results of the one-way Anova test are presented in Table 4. In Table 4, the results of the one-way ANOVA test are presented with a significance value of 0.466, which is more than 0.05 ($p > 0.05$). The research hypotheses used were H0, which states that giving propolis does not have an effect on reducing blood sugar levels, and H1, which states that giving propolis has an effect on reducing blood sugar levels. Based on the one-way ANOVA test, Ho was accepted, indicating that there is no significant difference between the groups. To determine the differences between the tested groups, the Mann-Whitney test was conducted. The results of the Mann-Whitney test are presented in Table 5.

**Table 5.** Mann-Whitney Test between Group

| Group | Sig. | Interpretation |
|---|---|---|
| Positive Negative | 0.021 | Different Meaning |
| Treatment Positive | 0.149 | No meaningfully different |
| Treatment Negative | 0.663 | No meaningfully different |

Table 5 presents the results of the Mann-Whitney test between groups. The treatment control group experienced a decrease in blood sugar levels that differed from that of the positive control group. However, when compared to the negative control group, the reduction in blood sugar levels in the treatment control group was similar.

*Discussion*

After receiving an induction of 20% D-glucose, all groups experienced a significant increase in blood sugar levels. This induction causes hyperglycemia in mice, according to a study by Suliska et al. (2020). The positive control used was glibenclamide 5 mg/kgBW, an antidiabetic drug used in type 2 DM therapy, as described in a study by Kulsum et al. (2022). The negative control was CMC-Na 0.25%, and the treatment control was propolis liquid extract 300 mg/kgBW. The use of glibenclamide as a positive control was intended to compare its effectiveness to the treatment of propolis liquid extract in reducing blood sugar levels. All groups showed a decrease in blood sugar levels, with significant differences between the positive and negative controls. However, there was no significant difference between the treatment group and the positive control or negative control groups after therapy was administered for 30 minutes. The propolis liquid extract used in the treatment group was found to have hypoglycemic activity and can reduce blood sugar levels in mice induced by 20% D-glucose. However, its hypoglycemic activity is not significantly different from that of the negative control group, indicating that the hypoglycemic activity of propolis extract is similar to CMC-Na. There was no significant difference between the treatment group and the positive control group, showing that the decrease in blood sugar levels was not similar to that achieved with glibenclamide. It is hoped that propolis extract will have similar working activities as glibenclamide, given the flavonoid content in propolis that can stimulate beta cells located in the Isle of Langerhans and cause increased insulin secretion, as described in a study by Alassaf et al. (2021). Glibenclamide stimulates insulin secretion from the

granules of pancreatic β-cells through its interaction with ATP-sensitive potassium channels in the cell membrane and opens $Ca^{2+}$ ion channels, causing the entry of $Ca^{2+}$ ions into pancreatic β-cells and stimulating insulin secretion, according to a study by Widyastuti et al. (2022).

Propolis liquid extract contains a variety of secondary metabolites, including alkaloids, flavonoids, tannins, triterpenoids, and quinones, as determined by phytochemical screening. However, saponins were not found. The presence of flavonoids, chlorogenic acid, cinnamic acid, ferulic acid, and phenethyl caffeic acid esters in propolis liquid extract accounts for its hypoglycemic effect, according to Randalinggi (2012). Flavonoids in propolis act as hypoglycemic agents by inhibiting aldose reductase and have a hypoglycemic activity similar to glibenclamide. Additionally, flavonoids act as antioxidants, reducing oxidative stress, regenerating islet cells, and repairing pancreatic tissue damage caused by free radicals (Raydian et al., 2017).

Flavonoids have three mechanisms of action as hypoglycemics: astringents precipitate proteins on the intestinal mucous membrane to form a protective layer that inhibits glucose uptake, accelerate the release of glucose from circulation for renal filtration and excretion, and increase metabolism or store glucose in fat deposits, which involves the pancreas producing insulin (Suhendi et al., 2015). To achieve a hypoglycemic effect, the recommended dosage of propolis extract is 200–300 mg/kg BB (Cunha et al., 2023).

The test results indicated that a dose of 300 mg/kgBW of propolis liquid extract could reduce the blood sugar levels of mice induced by D-glucose by 20%. However, it did not show a significant difference compared to glibenclamide, which was administered at a dose of 5 mg/kgBW. To determine the effective dose as an antihyperglycemic, it is necessary to vary the dose of liquid propolis extract that will be tested.

## Conclusion

The Mann-Whitney statistical analysis was used to determine the results, revealing that the water extract of propolis at 300 mg/kgBW did not have a significant effect on reducing blood sugar levels in animals induced by a 20% D-glucose solution, with a significance value ($p< 0.05$).

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**Author Contributions**
Article writing, A. F. N. M., A. R. S.; test suspension, N, I.; phytochemical screening, A. F. N. M.; glucose induction, A. F. N. M., H. F. A., S. S., N. I.; administration of test suspension, P. S. I.; data analysis, H. H. L., A. F. N. M.; project administration, S. S., N, I.; research preparation, P. S. I., N, I., A. F. N., S. S., H. F. A.; research supervisor, P. S. I.; funding acquisition, A. R. S.

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**Conflicts of Interest**
The authors declare no conflict of interest.

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