ISSN 3031-0911

The Effect Of Ethanol Ants Nest Extract (*Myrmecodia pendans*) On Fasting Blood Sugar Levels In Mice Obesity With Type 2 Diabetes

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Abstract

The Ant's Nest plant (*Myrmecodia pendans*) is known to have the potential to reduce blood glucose in obese patients with T2DM because it contains high flavonoids and tannins that can prevent oxidative stress and inhibit the work of lipase enzymes, pancreatic β cells, Glut-2 and α-glucosidase. This study aims to determine the effect of Ethanol Ants Nest Extract (*Myrmecodia pendans*) on changes in fasting blood glucose with T2D obesity. The type of research is true-experimental with pre-posttest control group design. This study used 30 male Wistar rats aged 8 weeks weighing 150-200 grams. The rats were divided into 6 groups, namely: KNo (normal control), KN (T2D obesity), KP (T2D obesity given metformin), P1, P2, and P3 (T2D obesity given ethanol ants nest extract 150mg/KgBW/day, 300mg/KgBW/day, and 600mg/KgBW/day for 14 days by gastric sonde). Data were analyzed using a Paired t-test and continued by using One-way ANOVA. There was a decrease in fasting blood glucose after 14 days of intervention, which was highest in the P3 group with a fasting blood sugar level of 177,534 ± 4.0 mg/dL ($p < 0.0001$). Giving ethanol ant nest extract has an effect in reducing fasting blood glucose levels.

Keywords: Ants Nest, Diabetes, Ethanol Extract, Fasting Blood Sugar, Obesity

Introduction

Obesity is the primary factor that triggers Type 2 Diabetes Mellitus (T2DM) and its complications. Diabetes mellitus is a chronic metabolic disorder characterized by high blood sugar levels associated with impaired insulin resistance and secretion (Soelistijo, 2021). According to the International Diabetes Federation (IDF), in 2021, there will be around 537 million individuals, or 10.5% of the total number of adults worldwide, suffering from DM. It is estimated that the number of people with DM will increase to around 643 million in 2030 and 783 million in 2045 in the adult age group between 20 and 79 years. According to WHO, the most significant increase in DM sufferers occurred in Southeast Asia, including Indonesia, which ranked 5th at 19.5% (Amalia *et al*., 2022).

The World Health Organization (WHO) estimates that in 2030, diabetes will become the 7th cause of death in the world. According to Suwinawati *et al*. (2020), 90 - 95% of the disease burden that causes 70% of deaths from diabetes cases worldwide is T2DM due to an unhealthy lifestyle. The number of patients is increasing due to the need for more knowledge of T2DM management. Information data, 2020 notes that the prevalence of DM in the 2018 Riskesdas in the Papua region was 1.1%, while compared to the West Java, Central Java, and East Java regions, it was 1.7%, 2%, and 2.5%. According to Soelistijo (2021), a person is categorized as having diabetes mellitus if the fasting blood glucose level is ≥ 126 mg/dl, blood glucose 2 hours after oral glucose tolerance test (TTGO) ≥ 200 mg/dl, blood glucose during ≥ 200 mg/dl with classic complaints and HbA1C ≥ 6.5%.

Current treatments are pharmacological as well as non-pharmacological. Pharmacology is antidiabetic drugs such as glinide, metformin, and others. Non-pharmacology therapy refers to nutritional therapy, namely 3J (schedule, type, and amount) (Pratiwi *et al*., 2018). Long-term use of multiple diabetes drugs has dangerous side effects for sufferers, such as weight gain (BW), insulin allergies, digestive disorders, frequent flatus (farting), and genital and urinary tract infections. It can trigger ketoacidosis (Soelistijo, 2021).

People today prefer alternative medicine, namely traditional medicine. A plant from Papua, the Ant's Nest, is a typical Indonesian plant considered a traditional medicine with various benefits but has yet to be clinically tested. Ant Nest is rich in antioxidants, namely flavonoids and tannins, with an IC50 value of 8.18 ppm, and in the Ethanol Extract of Ant Nest (EANE), the IC50 value is 32.48 ppm (very strong) (Mardany *et al*., 2016). This content can not only be a free radical antidote but also an anti-inflammatory, antimicrobial, and anti-inflammatory (Khairiah *et al*., 2019). Flavonoids and tannins play an essential role in preventing diabetes and obesity. Flavonoids preserve pancreatic β-cells and restore the sensitivity of cellular insulin receptors, maximizing insulin sensitivity. The flavonoid compound quercetin it contains inhibits GLUT2 of the intestinal mucosa, thereby lowering glucose. Other compound levels such as

ISSN 3031-0911

luteolin, rutin, apigenin, kaempferol, α-tocopherol, tannins, and stigmasterol are used to regulate blood sugar, increase insulin production, and inhibit α-glucosidase enzyme activity in the gut (Taebe *et al*., 2012).

Based on the background description above, the purpose of this study is to examine the effect of anthill ethanol extract in reducing fasting blood glucose levels in obesity with T2DM. The benefits obtained are to provide information on the benefits and effective dose of anthill ethanol extract in reducing GDP in obesity with T2DM. It is hoped that it can be used as a reference for further research to be applied in humans.

Methods

The type of research used is true-experimental, which aims to see the effect of giving ethanol extract of ant nest on fasting blood glucose, with a pre-posttest research design using a control group. This study was conducted from May to June 2022 at the Laboratory of the Center for Food and Nutrition Studies (PSPG), Gadjah Mada University, Yogyakarta. This study has received approval from the Research Ethics Committee of the Faculty of Medicine, Sebelas Maret University, with number 108/Un27.06.11/KEP/EC/2023.

The manufacturer of Ethanol Extract Ant Nest goes through the initial process of stripping the ant nest based on the inclusion and exclusion criteria that have been set, then cutting it into pieces to make it easier to dry quickly in the sun until it is not wet and dry to be thin like crackers and then blended to become coarse powder. The next step is the maceration method and modification (Ahmad & Risna, 2011), namely as much as 300 grams of coarse powder of ant nest that has been added with 70% ethanol in a ratio of 1:7. The immersion treatment is tightly closed using a bottle container which is then allowed to stand for 2 days with 1x stirring. Then, the macerate obtained is distilled/evaporated using soxhlet at a maximum temperature of 78oC so that the extract is not damaged.

Wistar rats used in this study were treated and raised in the Laboratory of the Center for Food and Nutrition Studies (PSPG), Gadjah Mada University, Yogyakarta. The sampling technique was purposive sampling with 30 samples, 8 weeks old, 150-200gram weight. Rats were adapted within 7 days with drinking water ad libitum, and comfeed feed. After the rats were adapted for 7 days, the rats were made obese, namely induced with HFHF diet for 14 days given 2 times (morning and evening) ad libitum (Maigoda et al., 2016). After 14 days, it was then measured by the lee index. After the mice were obese, the mice were induced with streptozotocin (STZ) 45 mg/kg BW/day and nicotinamide (NA) 110 mg/kg BW/day for 72 hours. Induction of STZ + NA into the abdominal cavity because in the abdominal cavity, there are many blood vessels, so hyperglycemia will occur. Rats are hyperglycemic if blood glucose is> 250 mg/dl (Maigoda et al., 2016). Experimental animals were divided into 6 groups, namely: KNo (standard control), KN (T2DM obesity), KP (T2DM obesity given metformin), P1, P2, and P3 (T2DM obesity), P1, P2, and P3 (DM given ethanol extract of ant nest 150mg/KgBW/day, 300mg/KgBW/day, and 600mg/KgBW/day.

Blood sampling was performed 2 times after STZ-NA induction to measure post-induction GDP levels in rats in fasting conditions ≥ 8 hours after 14 days of treatment. The number of days required for STZ-NA induction is 3 days. Blood samples were taken by first preparing the rats to be taken blood. Blood was then taken in the orbital sinus through vascularization. Second, prepare supporting equipment to take blood samples (1mL syringe and Eppendorf). Third, the rat is held by the nape of the neck and massaged with fingers. Fourth, the microhematocrit was scraped on the medial canthus. Blood was taken as much as 1mL and collected in Eppendorf (Nugroho, 2018).

The examination of GDP levels was carried out after rats were induced by STZ and NA quantitatively by the GOD-PAP method. Examining GDP levels by preparing rat blood plasma samples, stored in tubes containing 10% EDTA, centrifuged at 4000 rpm for 10 minutes. Plasma sample solution was taken as much as 10 µl added with 1000 µl of GOD-PAP reagent and incubated for 20 minutes, then the results were read on a spectrophotometer λ 500 nm (Nesti & Baidlowi 2017). The formula for calculating GDP levels is below:

Fasting blood sugar = sample absorbance (nm) / standard absorbance (nm) x standard glucose level (mg/dl)

Statistical data analysis using SPSS 26, where the normality test uses paired t-test parametric test, and homogeneity test using Levene. The test used to determine group differences is continued using ANOVA (Analysis of Variance).

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Results and Discussions

The data in **Table 1** shows that the average Body Weight (BW) value before any treatment was carried out, then after induction of the HFHF di*et, al*l groups of rats increased. Then, in the next group, after the induction of STZ-NA, the weight of the rats decreased in all groups except in the control group, which was not given any treatment at all/healthy. In the table, the average BW after being given EANE in the first week and week 2 increased except in the negative group, namely in the obese group with T2DM, who were not given any drugs. When viewed through paired t-test, results show that in all groups, there are significant differences, with the lowest decrease being in group 1, then group 2, and finally group 3.

Table 2. Blood Glucose Levels of Rats During Intervention

Group	Mean ± SD			P^b
	Initial GDP (mg/dl)	Final GDP (mg/dl)	Δ GDP (mg/dl)	
KNo	71,51 ± 1,88	73, 06 ± 2,61	1,55 ± 0,99	0,025
KN	255,30 ± 3,72	257,93 ± 2,63	2,63 ± 2,15	0,052
KP	257,96 ± 4,27	88,56 ± 2,46	169,40 ± 3,99	0,000
P1	260, 84 ± 8,61	118, 82 ± 3,01	142,02 ± 9,45	0,000
P2	265, 07 ± 2,56	101,85 ± 3,25	163,23 ± 6,41	0,000
P3	261,82 ± 4,39	84,28 ± 1,56	177,53 ± 4,09	0,000
P^a	0,00	0,00	0,00	

KNo : Group of normal/healthy experimental animals.
KN : Type 2 Diabetic obesity trial group.
KP : Type 2 Diabetic obesity trial group + metformin 9mg/200gBB
P1 : Type 2 Diabetic obesity trial group + Ethanol Ants Nest Extract 150mg/KgBW.
P2 : Type 2 Diabetic obesity trial group + Ethanol Ants Nest Extract 300mg/KgBW.
P3 : Type 2 Diabetic obesity trial group + Ethanol Ants Nest Extract 600mg/KgBW.
P^a *: (p<0,05) Uji One Way Anova.*
P^b *: (p<0,05) Uji Paired T-test*

Based on the results of statistical tests to determine the effect of EANE administration in reducing GDP levels. In Table 2, it can be seen that there was a decrease in GDP in the P1 group by 142.02 ± 9.45 ($p < 0.0001$), P2 by 163.23 ± 6.41 ($p < 0.0001$), and in the P3 group by 177.53 ± 4.09 ($p < 0.0001$), in the KNo group where the rats were in normal condition ($p=0.025$) and KN rats negative control group ($p=0.052$) showed no significant decrease in GDP levels. Based on the ANOVA test, it was found that there was a significant difference between the treatment groups ($p<0.0001$).

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KNo : Group of normal/healthy experimental animals
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KP : Type 2 Diabetic obesity trial group + metformin 9mg/200gBB
P1 : Type 2 Diabetic obesity trial group + Ethanol Ants Nest Extract 150mg/KgBW
P2 : Type 2 Diabetic obesity trial group + Ethanol Ants Nest Extract 300mg/KgBW
P3 : Type 2 Diabetic obesity trial group + Ethanol Ants Nest Extract 600mg/KgBW
P^a *: (p<0,05) Uji One Way Anova*
P^b *: (p<0,05) Uji Paired T-test*

In the results of the study, it was found that the manufacture of obese mice models with T2DM was successfully carried out. The manufacture of obese model rats uses the HFHF diet, while the T2DM manufacture model uses STZ-NA. The administration of STZ-NA can cause an increase in GDP levels as light as the decrease in BW from before in rats (hyperglycemia). Mice are said to be obese and have T2DM if the Lee index is more than 300, and mice are said to be hyperglycemia if blood glucose is> 250 mg/dl. GDP levels in all groups > 150 mg/dL. This is due to previous

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research that says rats are said to have DM if the GDP value reaches > 150 mg / DL after 72 hours of STZ-NA induction (Ortiz-Andrade *et al*., 2008). Administration of STZ-NA causes damage to pancreatic β-cells, causing a decrease in insulin levels and an increase in blood glucose levels/hyperglycemia. Streptozotocin has a toxic effect, thus the need for Nicotinamide (NA) as a protective substance in manufacturing animal models of type 2 diabetes. The NA-STZ induction type 2 diabetes model has various advantages, namely the existence of stable hyperglycemia without the need for exogenous insulin to survive, insulin stores in the pancreas up to 60%, reducing pancreatic beta cells (-40%) and glucose intolerance, mainly due to impaired insulin secretion. Induction of experimental animals using a combination of nicotinamide (NA) and streptozotocin shows a model of Type 2 DM disease and is more beneficial because it can measure the effects of both antidiabetic and other compounds characterized by a decrease in body weight in obese T2D patients (Ghasemi *et al*., 2014).

The results showed that the administration of EANE using 3 different doses, namely P1, P2, and P3 (150mg/KgBW/day, 300mg/KgBW/day, and 600mg/KgBW/day) had different results. This can be seen from the research data before and after the intervention. The results obtained in the positive group and all treatments significantly have an effect in reducing the blood sugar levels of obese rats with T2DM. The average results of the study in treatment groups 1, 2, and 3 obtained significant results. The results of the GDP value levels 1, 2, and 3 have sequentially significant results according to the increasing dose of EANE. Then, when compared to using a positive group, the results of the difference are higher in the group with the 3rd dose, so it can also be concluded that the effectiveness of the dose of EANE with an amount of 600mg / KgBW is more effective than using metformin drugs in Wistar rats induced with STZ-NA with obesity models with T2D. This is because the anthill plant can reduce blood sugar levels in test animals. After all, it can control blood glucose levels by stimulating pancreatic β-cells to secrete more insulin, inhibiting the work of the α-glucosidase enzyme so that the absorption of glucose in the intestine is inhibited, reducing impaired renal function, and increasing the solubility of blood glucose so that it is quickly excreted through urine (Taebe *et al*., 2012).

The positive control in this study used was metformin. The selection of metformin is a prevalent drug used for people with DM. Metformin has been proven to reduce mortality due to DM because it can maximize insulin sensitivity and reduce the risk of hypoglycemia and cardiovascular disease. It is one of the hypoglycemic agents and can lower blood glucose. The mechanism of metformin in the body is to improve the sensitivity of hepatic and peripheral tissues to insulin without affecting insulin secretion. This effect occurs due to the activation of kinases in the cell (AMP-activated kinase). In addition, metformin increases glucose utilization by intestinal cells, thereby lowering blood glucose, and is thought to inhibit glucose absorption in the intestine after food intake (Mongi *et al*., 2019). The delta results or the difference in the mean of the positive control group are similar. They can be said to be equivalent in function because of the different ways of working, but when compared, the results are better in treatment group 3, which is given EANE with an amount of 600mg / KgBW.

The effectiveness of anthill ethanol extract is because the anthill plant material contains a lot of active compounds, both antioxidants, including flavonoids, phenolic compounds, tocopherols, polyphenols, tannins, and other minerals that are useful as antimicrobials (Sudiono & Revana, 2020). Antioxidants are used as free radical neutralizers in normal cells. Patients with DM easily experience oxidative stress, which causes diabetic complications. Antioxidants are used as free radical neutralizers in normal cells. Patients with DM easily experience oxidative stress, which causes diabetic complications (Putriningtyas, 2013). It was also found that flavonoids contain 313 ppm tocopherol, which can reduce 96% of free radicals at a concentration of 12 ppm (Tatukude *et al*., 2014). Ant nests contain high antioxidants, namely flavonoids and tannins, with an IC50 value of 8.18 ppm, and in the Ethanol Extract of Ant Nests (EANE), the IC50 value is 32.48 ppm (very strong) (Mardany *et al*., 2016).

These results align with research conducted by Kurniawati & Sianturi (2016), which states that anthill plants contain various active compounds, one of which is flavonoids, which are helpful as antidiabetic therapy and can reduce blood sugar levels. Flavonoid compounds are red, purple, and blue pigments commonly found in plants. Flavonoids are protective against β-cell damage as insulin producers and can increase insulin sensitivity. Antioxidants can suppress beta cell apoptosis without altering the proliferation of pancreatic beta cells. The ability of flavonoids, especially quercetin, to inhibit GLUT 2 in the intestinal mucosa can reduce glucose absorption. This leads to a reduction in the absorption of glucose and fructose from the intestine, resulting in lower blood glucose levels. Glucose Transporter-2 is thought to be the primary transporter of glucose in the intestine under normal conditions. In a study conducted by Ayda (2023), it was found that flavonoids can inhibit glucose absorption. When quercetin was ingested with glucose, hyperglycemia significantly decreased. In addition, the mechanism of action of flavonoids in reducing blood sugar levels is through the inhibition of phosphodiesterase, which will then secrete insulin through the Ca2+ pathway by

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inhibiting phosphodiesterase so that cAMP levels in pancreatic beta cells increase. This will stimulate insulin secretion through the Ca2+ pathway, where the increase in cAMP will cause the closure of the ATP K+ channel in the beta cell plasma membrane. This situation results in membrane depolarization and the opening of the Ca2+ channel so that Ca2+ ions enter the cell and cause insulin secretion by pancreatic beta cells. Another role of flavonoids is to inhibit damage to Langerhans islet cells in the pancreas continuously so that pancreatic beta cells can repair themselves. It can increase the sensitivity of cell insulin receptors by closing and inhibiting K+ channels that stimulate insulin release so that they can cause a decrease in blood glucose levels and hypoglycemic activity. The above is how EANE works to reduce GDP levels in obese rats with T2DM, which can be seen in **table 2.**

Tannin compounds are known to have a hypoglycemic effect by increasing glycogenesis as an astringent and have a protective effect by acting as a free radical catcher and being able to activate antioxidant enzymes (Anggraini, 2020). The role of tannin content can also be seen because it functions as an astringent that can wrinkle the epithelial membrane of the small intestine, thereby reducing the absorption of food juice so that glucose absorption decreases (Raya *et al*., 2016). Another function of tannins is to spur glucose and fat metabolism so that the accumulation of calories in the body decreases, which results in a decrease in cholesterol levels. Tannins work in a direct way, namely the β-subunit insulin receptor, which then activates p13 kinase, which will stimulate the translocation of glucose transporter-4 (GLUT-4), which then stimulates glucose absorption and incorporates glucose into adipocyte tissue (Putriningtyas, 2013). Tannins are compounds that have a role in reducing body fat and weight. Because, in general, tannins can inhibit various aspects of the digestive process, tannins can reduce appetite so that it can lose weight. Tannins easily bind to proteins so that the impact can precipitate proteins that are on the surface of the small intestine, thus suppressing food absorption and being able to inhibit obesity. It was noted that the concentration of anthill ethanol extract with a concentration of 8.4% b/v reduced total blood cholesterol levels in male mice (Taebe *et al.*, 2012). In the research of Sukmawati *et al.* (2018), tannins can inhibit α-glucosidase, which is helpful in inhibiting glucose absorption after eating, thereby slowing down the state of postprandial hyperglycemia.

Conclusions

Ant nest ethanol extract was able to reduce GDP levels significantly. Dose 3 was the most effective dose using ethanol extract at 600mg/KgBB/day. Dose 3 can reduce GDP levels higher when compared to the positive group given the drug metformin. The results showed that ethanol extract could be considered antidiabetic therapy but still needs further research, such as acute cytotoxicity test and chronic cytotoxicity test. Ethanol extract of Ant Nest still needs to be recommended in humans because it still needs longer research.

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