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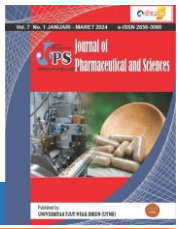

Test of antidiabetic effectiveness of nano herbal and ethanol extract of toppaspara leaves (*Mikania micrantha Kunth.*) on male white rats (*Rattus Norvegicus*) induced by *streptozotocin*

Uji efektivitas antidiabetes nanoherbal dan ekstrak etanol daun toppaspara (*Mikania micrantha Kunth*) Pada Tikus Putih Jantan (*Rattus Norvegicus*) yang diinduksi *streptozotosin*

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Abstract

Diabetes mellitus is a metabolic disease characterised by hyperglycemia caused by insufficient insulin production, insulin resistance, or both. The use of natural ingredients as a treatment option for diabetes mellitus can be developed as an alternative treatment, one of which is the toppaspara plant (*Mikania micrantha* Kunth.). The very small particle size in nano form is used to increase antidiabetic activity. Toppaspara leaves (*Mikania micrantha* Kunth.) have been empirically used as an antidiabetic, but this has not been scientifically proven. This research aims to determine the effectiveness of nanoherbal and ethanol extract of toppaspara leaves. This research was carried out experimentally, including the manufacture of simplicia, characterisation of simplicia, characterisation of nanoherbals and testing of antidiabetic effectiveness. Male white mice were induced with 2.5% streptozotocin intraperitoneally. Administration of 0.5% CMC suspension, nanoherbal and ethanol extract of toppaspara leaves at 50 mg/kgBB, 100 mg/kgBB, 200 mg/kgBB, metformin 45 mg/kgBB. The number of decreases in blood glucose levels is calculated; from the number of decreases in blood glucose levels, the percentage decrease in blood glucose levels is calculated. This analysis test uses One-way ANOVA followed by the Tukey test. The results of phytochemical screening of fresh leaves, simplicia ethanol extract and nano herbal toppaspara leaves contain secondary metabolite compounds such as alkaloids, tannins, flavonoids, saponins, steroids and glycosides. The results of the One Way ANOVA test and the Tukey test showed that nanoherbal 100 mg/kgBW and ethanol extract of toppaspara leaves 200 mg/kgBW were the best as antidiabetics and were not significantly different from metformin 45 mg/kgBW as a comparison.

Keywords*: *antidiabetic, toppaspara leaves, diabetes mellitus, nano herbal.

Abstrak

Diabetes melitus adalah suatu penyakit metabolik yang ditandai dengan hiperglikemia, yang disebabkan oleh kurangnya produksi insulin, resistensi insulin atau keduanya. Pemanfaatan bahan alam sebagai pilihan pengobatan diabetes melitus dapat dikembangkan sebagai salah satu alternatif pengobatan, salah satunya tanaman toppaspara (*Mikania micrantha* Kunth.). Ukuran partikel yang sangat kecil dalam bentuk nano dimanfaatkan untuk meningkatkan aktivitas antidiabetes.Daun toppaspara (*Mikania micrantha* Kunth.) secara empiris telah digunakan sebagai antidiabetes, namun belum terbukti secara ilmiah. Tujuan penelitian ini adalah untuk mengetahui efektivitas nanoherbal dan ekstrak etanol daun toppaspara. Penelitian ini dilakukan secara eksperimental meliputi pembuatan simplisia, karakterisasi simplisia, karakterisasi nanoherbal dan uji efektivitas antidiabetes. Pada tikus putih jantan yang diinduksikan dengan streptozotosin 2,5% secara intraperitoneal. Pemberian suspensi CMC 0,5%, nanoherbal dan ekstrak etanol

daun toppaspara dosis 50 mg/kgBB, 100 mg/kgBB, 200 mg/kgBB, metformin 45 mg/kgBB. Dihitung jumlah penurunan kadar glukosa darah, dari jumlah penurunan kadar glukosa darah dihitung persentase penurunan kadar glukosa darah. Uji analisis ini menggunakan *One Way* ANOVA dilanjutkan dengan uji Tukey. Hasil skrining fitokimia daun segar, simplisia ekstrak etanol dan nanoherbal daun toppaspara mengandung senyawa metabolit sekunder seperti alkaloid, tanin, flavonoid, saponin, steroid dan glikosida. Hasil uji *One Way* ANOVA dan uji Tukey bahwa pada nanoherbal 100 mg/kgBB dan ekstrak etanol daun toppaspara 200 mg/kgBB paling baik sebagai antidiabetes dan tidak berbeda nyata dengan metformin 45 mg/kgBB sebagai pembanding.

Kata Kunci: antidiabetes, daun toppaspara, diabetes melitus, nanoherbal.

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Introduction

Diabetes mellitus is a metabolic disease characterised by hyperglycemia caused by a lack of insulin production, insulin resistance, or both. [1]. Generally, diabetes mellitus (DM) is classified into type 1 DM and type 2 DM. Type 1 DM (insulin-dependent diabetes mellitus) is suffered by 5-10% of DM sufferers, occurs due to damage to pancreatic beta cells and causes lifelong insulin dependence, while type 2 DM (non-insulin-dependent diabetes mellitus) is suffered by 90-95% of DM sufferers, occurs due to insulin resistance, lack of insulin production, or both. [2].

The use of natural ingredients as a treatment option for diabetes mellitus can be developed as an alternative treatment. One of them comes from the toppaspara plant (*Mikania micrantha* Kunth.) with the local name sembung rambat [3]. *Mikania micrantha Kunth* is a climbing weed plant that belongs to the Mikania species of the Asteraceae family. [4]. *Mikania micrantha* Kunth is a plant native to South America and Central America which is used as an antibacterial, anti-inflammatory, antidiabetic, antihelminthic, and anticancer; this is because there are secondary metabolites in the *Mikania micrantha* Kunth plant, such as flavonoids, sesquiterpene dilactones (all parts of the plant) alkaloids, polyphenols, saponins, tannins (leaf parts) terpenoids (leaf and stem parts), and phenolics (root parts) [4].

The use of extracts as a treatment for diabetes can cause obstacles, namely patient non-compliance so that treatment becomes less effective. This is because the dose is large if formulated as an antidiabetic drug. In addition, drug delivery to reach target cells must go through microcirculation by blood capillaries or pores on various surfaces and membranes. [5]. Most holes, openings, and gates at the cellular or subcellular level are nanometer-sized. Therefore, nanoparticles are the most suitable for reaching the subcellular level. The adenosine monophosphate-activated protein kinase (AMPK) enzyme, which is the target of DM therapy, is found in the cytoplasm and can be achieved optimally at a particle size of 120-359 nm so that modification of the drug delivery system in the form of nanoparticles needs to be done to increase antidiabetic activity. [6].

The very small particle size is used to design and compose or manipulate materials to produce materials with new properties and functions. [7]Nanoparticles have advantages such as smaller particle

sizes, namely in the range of 1 - 1000 nm, which can increase drug absorption in the body, increase the activity of simple drugs, reduce doses, and minimise side effects. Therefore, simple drugs in the form of nanoparticles will be more efficient to use if made into antidiabetic drug preparations. [8].

Based on this, the researcher intends to utilise the simple leaves of toppaspara (*Mikania micrantha* Kunth) and prepare them in nanoparticles. This will make it more effective if used in the health sector to develop pharmaceutical preparations, especially in antidiabetic therapy.

Experimental Section

This study used experimental methods to find the effect of certain treatments on other groups under controlled conditions. [9]. The study includes collecting and preparing plant materials, characterising simple drugs, phytochemical screening, making extracts, making nano herbals, preparing experimental animals, and testing nano herbals and ethanol extracts on reducing blood glucose levels in male white mice. [10].

Materials

The materials used in this study were distilled water, streptozotocin, and Na.CMC (Sodium Carboxy Methyl Cellulose), ethanol, metformin, bismuth (III) nitrate, iron (III) chloride, lead (II) acetate, toluene, isopropanol, chloroform, glacial acetic acid, magnesium powder, chloral hydrate, 96% ethanol, potassium iodide, iodine, mercury (II) chloride, sulfuric acid, α-naphthol, ether, methanol, copper sulfate, potassium hydroxide, sodium potassium tartrate, hydrochloric acid, citrate buffer, distilled water and Toppaspara leaves.

Apparatus

The tools used consist of aluminium foil, laboratory glassware, a glucometer (Easy Touch®GCU strip test) and glucose test strip (Easy Touch®GCU strip test), object glass, cover glass, filter paper, drying cabinet, mortar and stamper, microscope, animal scale, electric scale, oral sonde, dropper pipette.

Manufacturing Simplicia Procedure

Fresh toppaspara leaf material is collected, washed thoroughly under running water, drained, and weighed (11,000 g). Toppaspara leaves are then dried in a drying cabinet at a temperature of 40-50°C until dry, and foreign objects remaining on the herbal medicine are removed during drying (dry sorting); after dry sorting, the herbal medicine is refined using a blender, the herbal medicine powder is then stored in a tightly closed plastic container that has been lined with parchment paper to prevent the effects of moisture and others.

Characteristics Check Of Simplicia

The characterisation process of the simplicia includes two parameters, namely specific and non-specific parameters. Specific parameters are macroscopic tests, microscopic tests, determination of ethanol-soluble extract levels, determination of water-soluble extract levels, and phytochemical screening. Non-specific parameters determine water content, ash content, and acid-insoluble ash content.

Leaf extract-making process

Making ethanol extract of toppaspara leaves is done by maceration using 96% ethanol solvent by putting 500 g of dry powder of the simplicia into a vessel, adding 5 L of 96% ethanol as a solvent. The maceration vessel is tightly closed and left for 5 days, protected from light, and stirred every few hours. The macerate is separated by filtration, and the dregs are dried in a cabinet. After drying, it is re-dissolved with 3.5 L of ethanol solvent and left for 3 days. All macerates are collected, and then the macerate obtained is concentrated with a rotary evaporator and then concentrated in a water bath for approximately 24 hours.

Making Nano Herbal

Making nanoherbal toppaspara leaves with the milling method using the Retsch E-max Ball Mill tool by inserting balls in the form of devices from the Retsch E-max Ball Mill tool as a crushing medium into a jar container with the Ball to Powder Ratio (BPR) commonly used is 1: 5, 1:10 and 1:20. For example, if the BPR

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is 1:10, it means 1 gram of sample and the weight of the ball used is 10 grams for the milling process. Furthermore, the jar containing the ball and sample is closed and turned on to rotate for 1 hour at a speed of 500 rpm.

Real sample analysis

The blood sugar level data were analysed statistically using one-way ANOVA analysis at a 95% confidence level, then a Post hoc Least Significant Difference (LSD) test was carried out to determine the significant differences between treatments, and the Tukey test was used to determine which differences were significant from the ANOVA test results by comparing the average of each group in pairs. Analysed using the SPSS (Statistical Product and Service Solution) program.

Results and Discussion

Blood glucose level calculation results

The increase in blood glucose levels is caused by induction with streptozotocin in mice. To see the increase in blood glucose levels after induction, orientation was carried out on the third day after induction, and the average blood glucose levels in each group were seen. The average data on the amount of increase in blood glucose levels before being induced with streptozotocin 2.5% can be seen in Table 2 and after being induced in Table 1 as follows:

Table 1. Average orientation data of blood glucose levels before and after induction

Before induction with streptozotocin		After being induced with streptozotocin on the 3rd day
Group	**KGD Amount**	**KGD Amount**
Group I	66,2	498,2
Group II	70,6	539,2
Group III	73,6	476,6
Group IV	72,8	490,8
Group V	74,2	486
Group VI	78	510,4
Group VII	75,8	496,4
Group VIII	71	461

Notes:
Group I : Suspensi Na CMC 0,5%
Group II : Suspensi NDT dosis 50 mg/kg bb
Group III : Suspensi NDT dosis 100 mg/kg bb
Group IV : Suspensi NDT dosis 200 mg/kg bb
Group V : Suspensi EEDT dosis 50 mg/kg bb
Group VI : Suspensi EEDT dosis 100 mg/kg bb
Group VII : Suspensi EEDT dosis 200 mg/kg bb
Group VIII : Suspensi metformin dosis 45 mg/kg bb

From the observation results in Table 1, it can be concluded that administration of streptozotocin with a concentration of 2.5% can increase blood glucose levels, proven by a significant increase after induction in mice. Therefore, a dose of streptozotocin 2.5% was chosen for further experiments. The increase in blood glucose levels is caused by β cells being destroyed through necrosis. After experiencing increased blood glucose levels, testing was done by administering nanoherbal and ethanol extract of toppaspara leaves at 50 mg/kgBW, 100 mg/kgBW, and 200 mg/kgBW. KGD examinations were conducted every 3 days from day 0 to day 15.

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Table 2. Average blood glucose level after administering the test material

KGD Amount After testing	Testing time (Day-)					
	Day -0	Day -3	Day -6	Day -9	Day -12	Day -15
CMC*	498,2	494	491	487	481	479
NDT** 50 mg/kgBB	539,2	419	243,6	139	71,8	
NDT 100 mg/kgBB	476,6	369,8	203	78,2		
NDT 200 mg/kgBB	490,8	274,6	140,4	72,8		
EEDT*** 50 mg/kgBB	486	401,8	299	234	185	118
EEDT 100 mg/kgBB	510,4	421,6	320,8	231,8	165,6	81,2
EEDT 200 mg/kgBB	496,4	351,8	209,8	81,8		
Metformin	461	251	130,4	69,60		

* : *Natrium Carboxy Methyl Cellulose*
** : nanoherbal daun toppaspara
*** : ekstrak etanol daun toppaspara

Based on the results of observations made using streptozotocin in Table 2, it shows that mice that have been induced experience an increase in blood glucose levels after giving the test material on the third day, there has been a decrease in blood glucose levels from various groups given the test material and a decrease in blood glucose levels is seen which is different from each group. The higher the dose of nano herbal and ethanol extract of toppaspara leaves given, the greater the decrease in blood glucose levels and the greater its effectiveness as an antidiabetic because the higher the dose given, the more secondary metabolite content will be.

Results of calculating the percentage of decreasing blood glucose levels

The percentage of decreasing blood glucose levels from various doses of nano herbal and ethanol extract of toppaspara leaves can be determined by calculating the percentage of decreasing blood glucose levels from the test material with the amount of decreasing blood glucose levels in the blank. The results can be seen in Table 3 as follows:

Table 3. Percentage decrease in KGD after administration of test material

Percentage decrease in KGD after testing	Testing time (Day-)					
	Day -0	Day -3	Day -6	Day -9	Day -12	Day-15
CMC*	0	0,97± 0,23	1,58± 0,41	2,60±0,39	3,53±0,77	4,46±0,55
NDT** 50 mg/kgBB	0	25,53± 5,64	62,97± 9,73	85,29±6,93	99,69±2,28	
NDT 100 mg/kgBB	0	26,59± 7,84	67,53± 7,83	98,95±1,36		
NDT 200 mg/kgBB	0	51,81± 5,55	83,92± 7,41	99,97±0,40		
EEDT*** 50 mg/kgBB	0	20,15± 5,26	44,68± 10,91	60,49±9,91	72,44±10,03	89,25±3,83
EEDT 100 mg/kgBB	0	20,99± 9,03	46,96± 10,05	64,08±8,17	79,19±8,58	99,33±3,38
EEDT 200 mg/kgBB	0	34,17± 9,30	68,02± 5,73	98,47±2,65		
Metformin	0	53,70± 3,40	84,67± 6,12	100,52±1,08		

* : *Natrium Carboxy Methyl Cellulose*
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Table 3 shows that the highest percentage of blood glucose level reduction is a nanoherbal dose of 200 mg/kgBW. In the group given nano herbal toppaspara leaves, the percentage of blood glucose level reduction was higher when compared to ethanol extract of toppaspara leaves, seen in nano herbal toppaspara leaves dose of 100 mg/kgBW and dose of 200 mg/kgBW, and ethanol extract of toppaspara leaves dose of 200 mg/kgBW showed the percentage of blood glucose level close to that of metformin dose of 45 mg/kg BW. Nanoherbal toppaspara leaves at 100 mg/kg BW are considered the most effective because a small dose already provides the same therapeutic effect.

ANOVA and Tukey statistical tests

The test results and blood glucose level reduction calculations showed significant differences between groups. To see significant differences between groups, an ANOVA test and a Tukey test were performed to see which groups were different and which were not. The results of the Tukey test can be seen as follows:

1. Test results on the 3rd day

   On the third day, all groups were significantly different from the negative control; EEDT 50mg/kgBW, EEDT 100 mg/kgBW, NDT 50 mg/kgBW, and NDT 100 mg/kgBW were not significantly different but significantly different from EEDT 200 mg/kgBW and NDT 200 mg/kgBW. All groups were significantly different from the positive control. The results can be seen in Table 4 as follows:

Table 4. Tukey test results day 3

Tukey HSD

Group	N	Subset for alpha= 0.05			
		1	2	3	4
"Negatif"	5	0.9680			
"EEDT 50mg/kgBB"	5		20.1560		
"EEDT* 100 mg/kgBB"	5		20.9860		
"NDT** 50 mg/kgBB"	5		25.5340		
"NDT 100 mg/kgBB"	5		26.5960		
"EEDT 200 mg/kgBB"	5			34.1680	
"NDT 200 mg/kgBB"	5			43.9186	
"Positif"	5				51.8140
Sig.		1.000	0.757	0.058	1.000

Means for groups in homogeneous subsets are displayed.

a. Uses Harmonic Mean Sample Size = 5.000.

* : ekstrak etanol daun toppaspara

** : nanoherbal daun toppaspara

2. Test results on the 6th day

On the sixth day, there was no significant difference between EEDT 50 mg/kgBW and EEDT 100 mg/kgBW, but it was significantly different from NDT 50 mg/kgBW and NDT 100 mg/kgBW. All groups were significantly different from EEDT 200 mg/kgBW. NDT 200 mg/kgBW was not significantly different from the positive control. The results can be seen in Table 5 as follows.

3. Test results on the 9th day

On the ninth-day test results, there was no significant difference in EEDT 50 mg/kgBW and EEDT 100 mg/kgBW, but there was a significant difference between EEDT doses of 50 mg/kgBW and 100 mg/kgBW with NDT 50 mg/kgBW. In NDT 50 mg/kgBW, there was a significant difference between NDT 100 mg/kgBW, EEDT 200 mg/kgBW, and NDT 200 mg/kgBW and positive control. NDT 100 mg/kgBW, EEDT 200 mg/kgBW, and NDT 200 mg/kgBW were not significantly different from the positive control. The results can be seen in Table 6 as follows:

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Table 5. Tukey test results day 6

Tukey HSD

Group	N	Subset for alpha= 0.05				
		1	2	3	4	5
"Negatif"	5	1.5740				
"EEDT* 50mg/kgBB"	5		43.4900			
"EEDT 100 mg/kgBB"	5		44.6740			
"NDT** 50 mg/kgBB"	5			62.9660		
"NDT 100 mg/kgBB"	5			67.5320		
"EEDT 200 mg/kgBB"	5				68.0160	
"NDT 200 mg/kgBB"	5					83.924
"Positif"	5					84.627
Sig.		1.000	1.000	0.970	0.057	1.000

Means for groups in homogeneous subsets are displayed.

a. Uses Harmonic Mean Sample Size = 5.000.

* : ekstrak etanol daun toppaspara

** : nanoherbal daun toppaspara

Table 6. Tukey test results day 9

Tukey HSD

Group	N	Subset for alpha= 0.05			
		1	2	3	4
"Negatif"	5	2.600			
"EEDT 50mg/kgBB"	5		60.4940		
"EEDT 100 mg/kgBB"	5		64.0820		
"NDT 50 mg/kgBB"	5			85.2860	
"NDT 100 mg/kgBB"	5				98.4680
"EEDT 200 mg/kgBB"	5				98.9440
"NDT 200 mg/kgBB"	5				99.9700
"Positif"	5				100.5140
Sig.		1.000	0.958	1.000	0.995

Means for groups in homogeneous subsets are displayed.

a. Uses Harmonic Mean Sample Size = 5.000.

Based on all the data obtained, it can be concluded that the NDT dose of 100 mg/kgBW, the NDT dose of 200 mg/kgBW, and the EEDT dose of 200 mg/kgBW are effective as antidiabetics. This can be seen on the 9th day of testing, which is not significantly different from the positive control.

Tukey test data processing was carried out until the 9th day because it was to see significant differences with positive controls. Secondary metabolites, namely flavonoids, influence effectiveness as an antidiabetic [11]Flavonoids have various bioactivities, including protecting against ultraviolet rays, inhibiting pigmentation, and protecting against various diseases. [12]. Antioxidants are one of the functions of flavonoids that can stabilise free radicals with radical reactive compounds to produce more stability, and non-flavonoids have an important role in preventing DM and its various complications. Based on experiments to prove the hypoglycemic effect of flavonoids, it can be concluded that plants containing flavonoids can lower blood sugar levels. [13]. Flavonoids have protective properties against β cell damage so that they can degenerate damaged pancreatic β cells, increase insulin sensitivity, and improve the performance of insulin receptors. [14]. Another mechanism is the ability of flavonoids, especially quercetin, to inhibit glucose absorption through GLUT 2 intestinal mucosa, which can reduce glucose absorption. Flavonoids can inhibit phosphodiesterase, which results in increased cAMP in pancreatic β cells. Increased cAMP will stimulate the release of protein kinase A (PAK) and increase insulin secretion. [15].

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Conclusions

The dose of nano herbal toppaspara leaves that provided the best anti-diabetic effectiveness was a dose of 100 mg/kgBW, and the dose of ethanol extract of toppaspara leaves that provided the best anti-diabetic effectiveness was a dose of 200 mg/kgBW. There was no significant difference on the ninth day between EEDT 200 mg/kgBW, NDT 100 mg/kgBW, and NDT 200 mg/kgBW with metformin. The best dose was NDT 100 mg/kgBW; this is because, at a small dose, the same therapeutic effect was obtained as the positive control. It is recommended that further researchers develop nanoparticle technology using other methods or in other dosage forms.

Conflict of Interest

All contributors have declared no conflicts of interest in this study. The research and article composition were conducted autonomously, without external influence, ensuring that no personal, financial, or professional interests have compromised the study's objectivity or credibility.

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