

SINGLE ANTIDIABETIC ACTIVITY AND COMBINATION OF AVOCADO LEAVES AND CURCUMA RHIZOME IN VIVO

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Abstract

Backgrounds; The prevalence of Diabetes Mellitus is increasing, meanwhile synthetic drugs use raw materials from abroad and undesirable events often occur. Indonesia is known to have thousands of plants with medicinal properties, including avocado leaves and ginger rhizomes which are empirically used by the Dayak people of South Kalimantan in the treatment of Diabetes Mellitus. Some of these empirical uses only use avocado leaves, only ginger rhizomes and some combine avocado leaves and ginger rhizomes and there is no uniform dosage dose; **Objectives;** Research purposes. Identifying the antidiabetic activity of avocado leaf extract and ginger rhizome alone or in combination. **Methods;** True experimental, Experimental test with Pre-Posttest Control Group Design. The samples used were 15 male Wistar rats and divided into 5 groups (n = 3), namely the positive group (Metformin 500 mg), the negative group (Na CMC 0.5%) and the treatment group, namely the Combination Formula Group (0.6 grams of ginger extract and 0.4 grams of avocado), Single Formula Group Temulawak Extract 17.5 mg/kgBB and Single Formula Group Avocado Leaf Extract 175 mg/kgBB given for 14 days. **Results;** The antidiabetic activity of the ethanol extract of ginger rhizomes was stronger than the ethanol extract of bay leaves, also against Metformin 500 mg. Formula 1 is a combination (0.6 gr of ethanol extract of ginger rhizome (*Curcuma xanthorrhiza* Roxb.) and 0.4 gr of avocado leaf (*Persea americana* P. Mill). has stronger antidiabetic activity than single ethanol extract of ginger rhizome or single ethanol extract avocado leaves also Metformin 500 mg. **Conclusions;** Single or combination of avocado leaf extract and ginger rhizome extract have antidiabetic activity.

Keywords: Antidiabetic, *Persea americana* P. Mill, *Curcuma xanthorrhiza* Roxb

BACKGROUND

Diabetes Mellitus is a serious, chronic, and complex metabolic disorder of multiple etiologies with profound consequences, both acute and chronic. It is a metabolic disorder characterized by high blood glucose, high insulin production, high insulin resistance and glucose or insulin intolerance. There are two main forms of diabetes, insulin-dependent Diabetes Mellitus (Type 1 Diabetes Mellitus, T1DM) and non- insulin-dependent Diabetes Mellitus, Type 2 Diabetes Mellitus (Sanjay, 2020).

Based on the 2018 National Basic Health Research, the prevalence of Diabetes Mellitus in Indonesia is 2.1% at ages > 15 years. The highest regions are Central Sulawesi (3.7%), North Sulawesi (3.6%) and South Sulawesi (3.4%). Meanwhile, the lowest was in Lampung Province (0.8%), then Bengkulu and West Kalimantan (1%) and Central Kalimantan (1.5%), and South Kalimantan (1%) (Dede M, 2017).

The prevalence of Diabetes Mellitus is increasing, meanwhile synthetic drugs use raw materials from abroad and undesirable events (side effects) often occur. Indonesia is known to have thousands of plants with medicinal properties, including avocado leaves and ginger rhizomes which are empirically used by the Dayak people of South Kalimantan in the treatment of Diabetes Mellitus. Some of these empirical uses only use avocado leaves, only ginger rhizomes and some combine avocado leaves and ginger rhizomes and there is no uniform dose. Irma Rahmayani's research in 2020 found that ginger rhizome extract at a dose of 17.5 mg/kgBB was the most effective in reducing blood sugar levels (Irma, 2020). Study Dea Septi Ulandari in 2022, avocado leaf extract at a dose of 175 mg/kgBB was the most effective in reducing blood sugar levels (Dhea, 2022). Mamik Anggraini's research in 2017, the combination of ginger rhizomes and avocado leaves at a dose of (0.6 gr: 0.4 gr)/kgBB, was the most effective in reducing blood sugar levels (Anggraini, 2017).

Therefore, local plants have been empirically/ethnomedicinally used for the treatment of Diabetes Mellitus. It is important to research to see the scientific data on the content of metabolite compounds that have the potential to act as antidiabetics from avocado leaves and ginger rhizomes and to examine them in vivo at dosages that are not toxic and have the best potential. The effect is equivalent to using synthetic drugs in treatment whether alone or in combination using diabetic Wistar rats by induction with Streptozotocin (Anggraini, 2017).

The research objectives are: Identifying the antidiabetic activity of avocado leaf extract and ginger rhizome alone or in combination.

METHODS

Correct research design experimental, True experimental, experimental test with Pre-Posttest Control Group Design. The samples used were 15 male Wistar rats and divided into 5 groups (n = 3), namely the positive group (Metformin 500 mg), the negative group (Na CMC 0.5%) and the treatment group, namely the Combination Formula Group (0.6 grams of ginger extract and 0.4 grams of avocado), Group Temulawak Extract Single Formula 17.5 mg/kgBB and Single Formula Group Avocado Leaf Extract 175 mg/kgBB given for 14 days. The stages carried out are:

1. Making extracts of ginger rhizomes and avocado leaves

Extraction uses the maceration method, simplicia powder of ginger rhizomes and avocado leaves is soaked using 96% ethanol for 3x24 hours. The residue obtained was filtered with flannel cloth. The filtrate obtained from the extraction results was evaporated

using a rotary evaporator at a temperature of 55°C and a speed of 60 rpm. This research was conducted under ETHICAL CLEARANCE No. 034/KEP- UNISM/XII/2023 from the Research Ethics Commission of Sari Mulia University Banjarmasin and Letter of Assignment from the Research and Service Institute of Sari Mulia University Banjarmasin number 2303/ST-Penelitian.I/LPPM/UNISM/XII/2023.

2. Preparation of 0.5% CMC-Na Test Preparation

Weighed 2.5 grams of CMC-Na powder, dissolved it in 500 mL of warm water using a magnetic stirrer. The dose given to control group mice was 12.5 mL/KgBW/day.

3. Metformin HCl

The dose of Metformin for the positive control group was 150 mg/KgBW/day. This dose is the result of the conversion of Metformin use from humans to mice. Making a stock of 12 mg/mL Metformin weighed 600.0 mg Metformin, crushed in a mortar, added 25 mL CMC-Na 0.5%, stirred homogeneously. Place in a 50 mL measuring flask.

4. Making ginger rhizome extract preparations

Preparing the ethanol extract of ginger rhizomes, weigh 3.5 g of ginger rhizome extract, put it in a mortar, then suspend it with 12.5 ml of CMC-Na 0.5%, stir until homogeneous. The suspension was transferred into a 25 mL measuring flask and 0.5% CMC-Na was added to the mark (Irma, 2020).

5. Making avocado leaf extract preparations

For making ethanol extract of avocado leaves, weigh 35g of avocado leaf extract in a mortar and then suspend it with 12.5 ml of CMC-Na 0.5%, stirring until homogeneous. The suspension was transferred into a 25 ml measuring flask and 0.5% CMC-Na was added to the mark (Dhea, 2020).

6. Making a combination of thick extracts from ginger rhizomes and avocado leaves

The preparation of ethanol extract of avocado leaves and ginger rhizomes was weighed (0.6 grams of ethanol extract of ginger rhizomes and 0.4 grams of ethanol extract of avocado leaves) put in a mortar then suspended with 12.5 mL of 0.5% CMC-Na, stirred until homogeneous. The suspension was transferred into a 25 mL measuring flask and 0.5% CMC-Na was added to the mark.

7. Acute Oral Toxicity Test

The acute oral toxicity test procedure refers to the OECD (Organization for Economic Co-operation and Development) Test Guideline No.420 with modifications (Limit Test). The test material in filtrate form is used as a whole, without the addition of solvents, and without going through a processing process so that the initial concentration is determined as 100%. According to the OECD (Organization for Economic Co-operation and Development) (2002), signs of sublethal toxicity can be observed from morphological changes, in this case the hair feels rough and untidy, the eyes, snout and tail look dirty. If signs of toxicity as mentioned above occur, the concentration is lowered (Christianti, 2014). Weight loss can indicate stress indicators and assess toxic symptoms that may occur because the toxic compounds contained in the test material can cause disturbances in the work of digestive enzymes so that they can reduce appetite which results in impaired growth of mice (Yan Hendrika, 2021). Acute oral toxicity studies were conducted starting at doses of 50 mg/kg, 100 mg/kg and 200 mg/kg evaluated for toxicity.

8. Test the antidiabetic activity of avocado leaf extract and ginger rhizome

Makes Rats suffer from Diabetes Mellitus Mice were induced by intraperitoneal injection of Steptozotocin at a dose of 70 mg/kg body weight, dissolved in 0.1 M cold citrate

buffer (pH = 4.5).

a. Human to Rat Dose Conversion

The dose is determined by dose conversion, the dose of Metformin used is 500 mg, so the dose conversion is:

Dose Conversion = *Human Dose x Rat Conversion Factor*

Conversion Dose = 5 mg x 0.018

Conversion Dose = 0.09 mg/200 grams Rat BW in 2.5 ml.

while the effective dose of avocado leaf extract is 175 mg/kgBB and ginger rhizome 17.5mg/kgBB and the combined dose is 6 (curcuma rhizome): 4 (avocado leaves).

b. Test Animals

1). Preparation of Test Animals

Test animals first adapt to the new environment. Acclimated for 7 days at room temperature (20-25°C) using 2 cycles (light and dark). Mice were given BR-2 food and drank water ad libitum.

2). Grouping Test Animals

Test animals were grouped into 5 groups:

Table 1. Test Animal Groups

No	Group	Treatment of mice
1	Control (-)	0.1% Na-CMC solution
2	Control (+)	Metformin 500 mg
3	Group I	Avocado leaf extract 175 mg/kgBB
4	Group II	Temulawak rhizome extract 17.5 mg/kgBB
5	Group III	Extract combination 6 (curcuma rhizomes):4 (avocado leaves)

3). Measurement of Diabetes Levels

Blood sugar levels were measured on day 1 after induction, day 7 and day 14 in 5 groups using the easy touch glucose device.

2. Phytochemical Test Screening..

a. Alkaloids

1 mL of extract filtrate of ginger rhizomes and avocado leaves, add 10 drops of H₂SO₄ N, add 3-5 drops of Dragendorff's reagent. If there are alkaloids, an orange-brown precipitate will form.

b. Flavonoids

1 mL filtrate of ginger rhizome extract and avocado leaves, add 2 drops of concentrated HCL, add magnesium. If there are flavonoids, foam or foam will form.

3. Determining avocado plants and ginger plants in the MIPA laboratory at Lambung Mangkurat University.

RESULTS AND DISCUSSION

1. Determination of Extract Standards

Results from making ethanol extract Temulawak rhizomes (*Curcuma xanthorrhiza* Roxb) and avocadoleaves (*Persea americana* P. Mill) are seen in the table below.

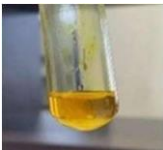

Table 2. Determination of extract standards

No	Making Extracts	Results	Unit
Determination of Standards for Temulawak Rhizome Extract			
1	Simplicity	262.52	Grams
2	Amount of solvent (ethanol 96%)	800	Milliliters
3	Thick extract	54.09	Grams
4	% Extract yield	20.6 %	%(w/w)
Determination of Avocado Leaf Extract Standards			
1	Simplicity	323.82	Grams
2	Amount of solvent (ethanol 96%)	1,2	Liter
3	Thick extract	50.9	Grams
4	% Extract yield	15.72 %	%(w/w)

According to research (Nahor *et al.*, 2020). The higher the yield value indicates that the extract produced is greater, this means that more nutritious substances are obtained and contained Roxb) has a higher yield than avocado leaf extract (Nahor, 2020).

2. Phytochemical Screening of Extracts

Table 3. Rhizome Flavonoid Test Curcuma and Avocado Leaves

Group Compound	Rhizome Curcuma	Leaf Avocado
Flavonoids Positive (+)	 Orange	 Orange

Based on the results in Table 2, both extracts positively contain flavonoids and alkaloids. The flavonoid test was carried out based on the Wilstater reaction. The flavonoid test on the ethanol fraction showed that it contained positive flavonoids because the solution changed color to orange (Pasaribu, 2021). The flavonoid test showed the presence of flavonoids with γ - benzopyrone as flavones, flavonols and isoflavones. The alkaloid test with Dragendorff's reagent produces a brownish orange precipitate. This is due to the reaction of the nitrogen atom in the alkaloid against the K⁺ metal ion in the potassium tetraiodobismutat (III) complex compound forming a potassium-alkaloid complex with coordinating covalent bonds and a tetraiodobismutat (III) complex ion (Wahyuni, 2021).

3. Acute Toxicity Test of Curcuma Rhizome and Avocado Leaf Extracts

Table 4. Acute Toxicity Test Results

Parameter	Dose	Day 1	Day 2	Day 3
Body temperature	50 mg	34.3C	34.5C	34.9C
	100 mg	34C	34C	33.6C
	200 mg	33.4C	34.2C	33.2C
Urination	50 mg	Normal	Normal	Frequent urination
	100 mg	Normal	Frequent urination	Frequent urination
	200 mg	Normal	Frequent Urination	Frequent urination
Hair	50mg	Smooth & Clean	Standing & Clean	Standing & Clean
	100mg	Smooth & Clean	Stand & Clean	Standing & Clean
	200mg	Smooth & Clean	Stand & Clean	Standing & Clean
Stool shape	50mg	Solid & Normal	Solid & Norm	Solid & Normal
	100mg	Liquid & Bright Color	Liquid & Bright Color	Liquid & Bright Color
	200mg	Solid & Normal	Liquid & Bright Color	Solid & Normal
Respiration	50mg	Normal	Normal	Normal
	100mg	Normal	Normal	Normal
	200mg	Normal	Normal	Normal
Behavior	50mg	Rats are active & do not show toxic symptoms	Rats are active & do not show toxicsymptoms	Rats are active & do not show toxicsymptoms
	100mg	Rats are inactive & do not show toxic symptoms	Rats are active & do not show toxicsymptoms	Rats are active & do not show toxicsymptoms

200mg	Mice were inactive and did not show toxic symptoms	Rats are active & do not show toxicsymptoms	Mice were active and showed notoxic symptoms
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The toxicity test of the extract of *Curcuma xanthorrhiza* Roxb and Avocado Leaves (*Persea americana* P. Mill) on test animals at doses of 50 mg, 100 mg and 200 mg for 3 days using the OECD method did not show any signs of toxicity in the test animals. This is based on the absence of signs of toxicity that appear after administering the test sample. This is made clear by the results in table 5, namely that there was no significant change in the shape of the feces of the test animals. The results also showed that no test animals died after exposure to the test samples and there were no significant changes in body temperature, urination, fur, respiration and behavior of the test animals. Results of acute toxicity testing (body temperature, urination, fur, respiration and behavior of test animals)

According to (K. Lukito *et al.*, 2022) Toxicity tests on test animals can be seen from the death rate of test animals, behavior, physical condition (skin, fur, eyes, mucous membranes), respiratory system, autonomic nervous system, central nervous system and somatomotor activity (Lukito, 2022).

4. Test the single extraction activity of ginger rhizomes, avocado leaves and combination

Table 5. Antidiabetic Activity Test of Temulawak Rhizomes

Group	Before induction (mg/dl)	Day 1 (mg/dl)	Day 7 (mg/dl)	Day 14 (mg/dl)
Control(-)	95	170	170	170
Control(+)	95	201	170	91
Formula 1	94	151	170	88
Formula 2	95	133	138	92
Formula 3	104	139	207	122

From the data obtained during 14 days of administering Curcuma Extract with treatment, it was found that blood glucose levels in Wistar rats decreased, where previously blood glucose levels in test animals increased after being given the Streptozotocin compound i.p. (intra peritoneal). Formula 1 (17.5 mg/kgBB) is able to lower blood sugar levels more strongly than positive control Metformin 500 mg for 14 days.

5. Single Antidiabetic Activity Test of Avocado Leaf Extract

Table 6. Antidiabetic Activity Test of Avocado Leaf Extract

Group	Before induction (mg/dl)	Day 1 (mg/dl)	Day 7 (mg/dl)	Day 14 (mg/dl)
Control (-)	95	170	170	170
Control (+)	95	207	170	91
Formula 1	86	127	173	100
Formula 2	102	256	117	105
Formula 3	104	205	138	97

From the data obtained during 14 days of administering avocado leaf extract through treatment, it was found that blood glucose levels in Wistar rats decreased, where previously blood glucose levels in test animals increased after being given the Streptozotocin compound i.p. (intra peritoneal). The ethanol extract of avocado leaves was able to reduce blood sugar levels for 14 days, but was weaker than the positive control of Metformin 500 mg for 14 days.

6. Antidiabetic Activity Test of Combination of Temulawak Rhizome Extract and Avocado Leaves

Table 7. Antidiabetic Activity Test of Combination of Temulawak Rhizome Extract and Avocado Leaves

Group	Before Induction (mg/dl)	Day 1 (mg/dl)	Day 7 (mg/dl)	Day 14 (mg/dl)
Control (-)	107.33	123.6	126.3	133
Control (+)	128.67	261	254	113
Formula 1	116	160	173	107
Formula 2	152	531	492	377
Formula 3	136	366	172	115

From the data obtained during 14 days of administering Curcuma and Avocado Leaf Extracts through treatment, it was found that blood glucose levels in Wistar rats decreased, where previously blood glucose levels in test animals increased after being given the STZ compound i.p. (intra peritoneal). Of the three treatments, Formula 1 with concentrations (0.6 g of Temulawak Rhizome Ethanol Extract and 0.4 g of Avocado Leaf Ethanol Extract) could significantly reduce blood sugar levels in Wistar rats more strongly than the positive control Metformin 500 mg given for 14 days.

The presence of antidiabetic activity can occur due to the presence of secondary metabolite compounds of flavonoids and alkaloids. Flavonoids have a mechanism of action by increasing glucose tolerance and inhibiting the activity of glucose transporters from the intestine so that they can reduce blood glucose by stimulating pancreatic β cells to release more insulin (Fadel, 2020).

Alkaloids have a regenerative mechanism of action that damages pancreatic β cells. Apart from that, alkaloids work to reduce blood glucose by pancreatic extract mechanism, namely by increasing glucose transport in the blood, inhibiting glucose absorption in the intestine, stimulating glycogen synthesis and inhibiting glucose synthesis (Rahayuningsih, 2020).

7. Data Analysis

Data from blood sugar measurements were tested using the Product and Service Statistics (SPSS) Program. Based on the results of the normality test, it was found that the group data for the initial fasting blood sugar examination was normally distributed, namely 0.254, while the other 4 measurement times were not normally distributed with a significance value of 0.003 for post-fasting blood sugar and a significance value of 0.00 on the seventh and fourteenth days. after streptozotocin induction. Followed by the Homogeneity Variance Test with a significance result of 0.507 so that the data is homogeneous. while the other 4 measurement times are not homogeneous. Meanwhile, the other 4 measurement times were not homogeneous with a significance value of 0.03 for blood sugar after fasting; 0.04 on the seventh day and 0.02 on the fourteenth day after induction with streptozotocin. Because the

fasting blood sugar data before being induced by Streptozotocin met the requirements for the Anova test, the P value was 0.015 (<0.05), so it can be concluded that there were differences in fasting blood sugar levels before treatment in the five treatment groups. To find out which groups are different, a post hoc test is then carried out as follows:

1. Fasting Blood Sugar Data for Rats Treated with Temulawak Ethanol Extract is different from Fasting Blood Sugar Data for Rats Treated with a Combination of Temulawak Extract with Avocado Leaf Extract (p value = 0.007).
2. Fasting Blood Sugar Data for Rats treated with Temulawak Ethanol Extract is different from Fasting Blood Sugar Data for Positive Control Rats (p value = 0.0017)
3. Fasting blood sugar data for rats treated with ethanol extract of avocado leaves is different from fasting blood sugar data for rats treated with a combination of ginger extract and avocado leaf extract (p value = 0.006).
4. Fasting Blood Sugar Data for Rats treated with Avocado Leaf Ethanol Extract is different from Fasting Blood Sugar Data for Positive Control Rats (p value = 0.015)
5. Fasting Blood Sugar Data of Rats with Combination Treatment of Curcuma Extract with Avocado Leaf Extract is different from Fasting Blood Sugar Data of Negative Control Rats (p value = 0.029)

CONCLUSION

It can be concluded that all formulas are a combination of ethanol extract of Curcuma Rhizome (*Curcuma xanthorrhiza* Roxb.) and Avocado Leaves (*Persea americana* P. Mill). there was a decrease in blood glucose levels on day 14 (has antidiabetic activity). Single-handedly, the antidiabetic activity of the ethanol extract of ginger rhizomes was stronger than the ethanol extract of bay leaves, also against Metformin 500 mg. Formula 1 is a combination (0.6 gr of ethanol extract of ginger rhizome (*Curcuma xanthorrhiza* Roxb.) and 0.4 gr of avocado leaf (*Persea americana* P. Mill). has stronger antidiabetic activity than single ethanol extract of ginger rhizome or single ethanol extract avocado leaves also Metformin 500 mg.

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