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Original Article

POTENTIAL OF KABAU LEAF ETHANOL EXTRACT (*ARCHIDENDRON BUBALINUM* (JACK.) I. C. NIELSEN) TO DECREASE OF BLOOD GLUCOSE LEVELS INDUCED ALLOXAN

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ABSTRACT

Objective: This study describes the potential antidiabetic activity of ethanol extracts of Kabau leaves (*Archidendron bubalinum)*

Methods: Extraction was done using the maceration method with 96% ethanol as solvent. The simplicia and extracts were characterized, screened for phytochemicals using Thin Layer Chromatography (TLC). Blood glucose levels were examined by GOD-PAP enzymatic method. Wistar rat was induced by alloxan (120 mg/kg BW i. p) to hyperglycemic condition, the dose variations of Kabau leaves extract i. e 250, 500, and 1000 mg/kg BW (p. o). The data was statistically tested using one-way ANOVA with a confidence level of ($p<0.05$).

Results: The phytochemical screening showed the presence of alkaloids, flavonoids, phenolics, monoterpenes and sesquiterpenes, steroids, and triterpenoids, saponins. TLC showed that the extract contained spots (Rf 0.45) which are suspected to be flavone glycosides, biflavonyls, and unusually substituted flavones. Phenolic compounds (Rf 0.225; 0.25; 0.325 and 0.45) were characterized by a color change to blackish green after being sprayed with $FeCl_3$. Saponin glycoside compounds (Rf 0.57) were characterized by the presence of purple spots after being sprayed with vanillin sulfate. Test animals in all test groups experienced hyperglycemia (>126 mg/dl) and a significant increase in blood glucose levels compared to the control group. MDA levels in test animals given a dose of 1000 mg/kg BW was 0.024±0.003.

Conclusion: Ethanol extract of Kabau leaves can reduce blood glucose levels in hyperglycemic rats by 33% at a dose of 1000 mg/kg BW. The results of one-way ANOVA ($p<0.05$) and Measurement of MDA levels in test animals was 0.024±0.003.

Keywords: *Archidendron bubalinum leaves,* Induced alloxan, TLC, GOD-PAP, and MDA

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INTRODUCTION

Diabetes mellitus is a metabolic disorder caused by a deficiency of the hormone insulin. Diabetes mellitus is caused by a decrease in the circulating level of insulin concentrations (insulin deficiency) and a decreased response of peripheral tissues to insulin (insulin resistance). Insulin deficiency can elevate plasma phospholipid and cholesterol concentrations due to excess fatty acids in plasma which also stimulates the conversion of a number of fatty acids into phospholipids and cholesterol in the liver whose concentrations will increase in the absence of insulin. High sucrose intake is generally considered a risk factor for obesity and insulin resistance. Administration of high levels of sucrose for 8 w can increase abdominal fat accompanied by hyperinsulinemia in male Wistar strain rats by reducing insulin sensitivity [1].

Kabau plant (*Archidendron bubalinum* (Jack) I. C. Nielsen), which is a genus with Jengkol (*Archidendron pauciflorum* (Benth.) I. C. Nielsen) [2, 3] and the same family as Chinese Petai (*Leucaena leucocephala* L.) [4] is thought to have activity in lowering blood glucose levels in white rats. Wistar strain males. Based on chemotaxonomy, plants in the same family and genus contain compounds with the same chemical structure framework, so they have the potential to have the same biological activity [5, 6]. The study conducted by [7] show that Kabau seeds had antidiabetic activity and showed that ethanol extract at a dose of 250 mg/kg BW was better with the glucose tolerance test method, with alloxan induction animal models and high-fat feed induction. The methanol fraction derived from 96% ethanol extract gave a good decrease in blood sugar levels in the screening method with the glucose tolerance test. Kabau seeds have the potential to have antidiabetic activity, so it is necessary to develop research from other plant parts, namely Kabau leaves in the hope that they can be used as alternative medicinal raw materials but do not have the odor present in Jengkol seeds.

MATERIALS AND METHODS

Plant materials

Research material in the form of Kabau leaves obtained from Gunung Sari Village, North Lampung, Lampung. Plant determination was carried out at the Research Center of the Indonesian Institute of Sciences (LIPI) Bogor number 408/IPH. I.01/If.07/II/2018, on 13 February 2018. Fresh leaves were sorted by wet sorting, then washed with running water, then the drying process is carried out. Simplicia was carried out by a characterization process to obtain standardized simplicia and phytochemical screening to determine secondary metabolites contained in simplicia Kabau leaves.

Animals

The experimental animals used in this study were Wistar strain male white rats with body weights of 150-250 g obtained from PT. Biofarma, use, and care for the experimental animals were approved by the Ethics Committee of Padjadjaran University (Approval no 114/UN6. KEP/EC/2019).

Methods

Extract preparation

Extraction was carried out by maceration of 600 g of simplicia with 6 l of 96% ethanol solvent, with solvent change 3 times 24 h. The liquid extract that has been collected is evaporated with a rotary evaporator at a temperature of 30-40 °C. Furthermore, in the evaporating dish, the macerate was evaporated at room temperature so that a thick extract was obtained. The ethanol extract was then analyzed qualitatively using Thin Layer Chromatography (TLC) using an eluent according to its polarity. The results of the chromatogram pattern were viewed under UV lamps 254 and 366 and the TLC plate was sprayed with chromogenic reagents for various secondary metabolites.

Glucose tolerance test

The rats were divided into six groups as follows: group I (normal group); group II (negative control, given 0.5% CMC Na); group III (positive control, given 0.45 mg/kg glibenclamide); group IV, V, VI (given Kabau leaf ethanol extract at 250 mg, 500 mg, 1000 mg. Fifteen minutes after oral administration of vehicle or test extract, each rat was given glucose at doses of 6.3 g/kg orally. Glucose levels were measured before the administration of the vehicle or test extract and at 15, 30, 60, 90, 120, and 180 min [8].

Determination of blood glucose concentration

Blood glucose level was measured by Easy Touch GCU glucose strip in type: ET-301 (Boehringer). The glucose levels were expressed in mg/dl. Blood glucose concentration from a sample taken from the tail vein was measured using the Easy Touch® blood glucose meter (Boehringer).

Antidiabetic testing an alloxan-induced diabetic model

Based on the results of the glucose tolerance test dose was chosen for testing in the alloxan-induced diabetic rat model. The rats were divided Into four groups: group I (normal group); group II (negative control, receiving 0.5% CMC-Na); group III (positive control, receiving 0.45 mg/kg BW glibenclamide); group IV (positive control group, receiving 4.5 mg/kg ascorbic acid); groups V, VI, VII, ethanol extract of Kabau at 250, 500 and 1000 mg/kg. A group of animals, before administering the test material/extract (excluding those in a normal group) were treated with 120 mg/kg alloxan for seven days. The rats that were used as a diabetic model were those with fasting glucose levels of>126 mg/dl and showed signs of polyuria and polydipsia. On day 15 the rats were sacrificed CO_2. Immediately afterward, 3 ml of blood was taken from the heart [9].

Measurement of glucose levels by the enzymatic method of glucose oxidase-phenol aminophenazon (GOD-PAP)

10 µl serum was mixed with 1000 µl glucose liquefaction reagents and incubated for 10 min at 20-25 °C. The absorbance of the reaction result was measured using a spectrophotometer at a wavelength of 510 nm. The data obtained is then processed using ANOVA analysis [10].

Measurement of MDA (Malondialdehyde) activity

200 µl serum from each rat was taken and then added with 2000 µl 20% trichloroacetic acid (TCA) and 2000 µl 0.067% thiobarbituric acid (TBA). The homogeneous solution was heated in a water bath for 10 min, and, once cooled, centrifuged at 3000 rpm for 10 min. The absorption of the colored solution formed was measured at a wavelength of 532 nm using UV-Vis Spectrophotometry [11].

RESULTS AND DISCUSSION

Yields of extraction

The extraction method used is the maceration method using 96% ethanol as solvent. The maceration method is used in order to maintain the secondary metabolite content contained in the simplicia because the nature of the secondary metabolite content is not known. Ethanol 96% was chosen because ethanol is a universal solvent that can dissolve almost all secondary metabolites contained in simplicia. From 600 g of Kabau leaf simplicia extracted with 6 l of 96% ethanol solvent, 40.93 g of thick extract were obtained and the yield of extracts was 6.821%.

Phytochemical screening of simplicia and extract

Phytochemical screening of Kabau leaves from South Sumatra revealed the presence of alkaloids, flavonoids, phenols, triterpenoids/steroids, mono-/sesquiterpenes, and saponins. The flavonoid results in an orange or yellow color change in the amyl alcohol layer. The addition of magnesium and hydrochloride powder reduces flavonoids and gives them a red color. Flavonoids are the largest group of phenolic compounds found in nature. Flavonoids can act as antioxidants and free radical scavengers because their hydroxyl groups donate hydrogen to free radicals [12]. A saponin compound was tested and the results were positive with bubbles 1-1.5 cm in height. This foam occurs due to the presence of hydrophilic groups that bind to water, while the hydrophobic ones bind to air [13].

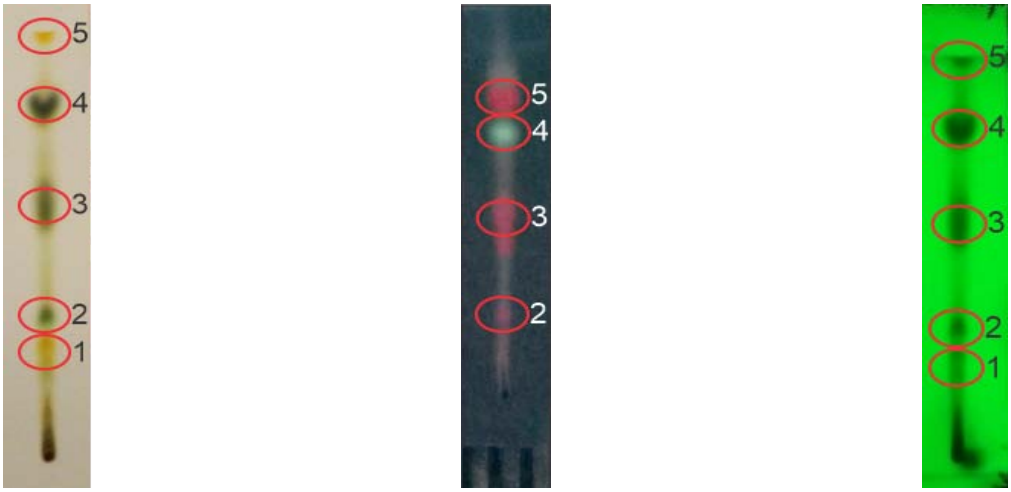
A positive result of the phenol test is indicated by a change from green-black upon reaction with $FeCl_3$. The color change is due to the presence of phenolic hydroxyl groups in the compound.

Alkaloid Screening with Ammonia and Chloroform is aimed at binding alkaloids in free form. Alkaline alkaloids dissolve in acidic solvents, so adding HCl has the effect of binding alkaloids together in the form of salts. Alkaloid compounds also have a nitrogen group with an unshared electron pair, which reacts with the Dragendoroff reagent to make the alkaloid compound nucleophilic (base). It has a nitrogen group with a lone pair of electrons, making the alkaloid compound nucleophilic (base). Meyer's reagent is intended to detect alkaloids, and the reagent binds to alkaloids to produce a white precipitate [14]. The terpenoid/steroid test is indicated by the formation of a red or green color when reacted with Liberman-Burchard, which indicates a positive steroid content. The results of the mono/sesquiterpene test were positive, a purple color was formed when reacted with vanillin sulfate. A positive quinone test is marked with a red color when reacted with 5% KOH.

In addition, when screening monoterpenoids and sesquiterpenoids, ether is added to attract monoterpenes and sesquiterpenes, vanillin sulfate is added to form a conjugated double-bond compound, and then H_2SO_4 hydrolyzes water. and reacts with an acetyl derivative to develop a color [15]. Based on the results of phytochemical screening, all the extracts and simplicia tested showed the same results.

Thin layer chromatography

Thin layer chromatography was carried out on the ethanol extract of Kabau leaves which aims to identify and determine the components of secondary metabolites. Prior to TLC, the stationary phase is silica gel and the mobile phase is toluene: chloroform: ethyl acetate (4: 5: 1). Before TLC, the mobile phase in the chamber is saturated. The reason for saturation before inserting the plate is to remove water vapor and prevent the pressure in the chamber does not affect the spot propagation process.



a **b** **c**

Fig. 1: (a) TLC results of Kabau leaf extract were seen in visible light, (b.) TLC results of Kabau leaves were seen at UV 366 nm, (c.) TLC results of Kabau leaves were seen at UV 254 nm

Table 1: Interpretation of the color formed on the spot from the Kabau leaf TLC

Spot	*Rf* value	Colour			Interpretation	Reff
		Visible	UV λ 366 nm	UV λ 254 nm		
6	0.875	Yellow	-	Black	β-Carotenoids	[16]
5	0.775	Dark green	Orange	Black	Chlorophyll	[17]
4	0.675	-	Light blue	-	-	
3	0.52	Grey	Orange	Black	Pheophytin-α	[17]
2	0.4	Yellowish Green	Orange	Black	Chlorophyll-b	[17]
1	0.225	Yellow	-	Black	Carotenoids	[16]

Furthermore, spray detection is carried out to ensure whether the compound is the desired compound using specific spray reagents for each compound. Spray detection results can be seen in table 2.

Table 2: Kabau leaf TLC results with spray reagent

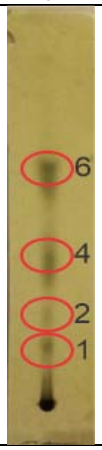
Not use chromogenic reagent			Chromogenic reagent		
Visible	UV λ366 nm	UV λ254 nm	Ammonia vapor	$FeCl_3$	Vanilin-H_2SO_4
					

Table 3: The color formed from the TLC of Kabau leaves after being sprayed with reagents

Spot	*Rf Value*	Not use chromogenic reagent			Chromogenic reagent			Interpretation	Literature
		Visible	UV λ 245 nm	UV λ 366 nm	Ammonia vapor	$FeCl_3$	Vanilin-H_2SO_4		
7	0.825	Yellow	Black	Dark purple	-	-	Yellow		
6	0.575	Dark green	Black	Dark purple	Orange	-	Purple	Saponins	[18]
5	0.45	-	-	-	Light Blue	Blackish green	Bright green	Flavonoids	[19]
4	0.395	Dark Green	Black	Dark purple	Orange	-	-		
3	0.325	-	-	-	Orange	Blackish green	Bright green		
2	0.25	Green	Black	Dark purple	Orange	Blackish green	-	Phenolic	[20]
1	0.225	Yellow	Black	-	Orange	Blackish green	Yellow brown		

Ammonia vapor was used to detect flavonoid compounds, TLC plate steamed with ammonia vapor under 366 nm UV lamp emitted light blue fluorescence, indicating the presence of isoflavones [21] The plate shows that the positive Kabau leaves contain flavonoid compounds with an Rf of 0.45.

$FeCl_3$ reagent is used to determine the content of phenolic compounds, which are marked by a color change to blackish green due to the complex formation reaction between the phenolic group and Fe [19]. TLC result viewed in visible light showed a color change after being sprayed with $FeCl_3$.

Vanillin sulfate reagent was used to detect saponin compounds. A positive result is indicated by a blue-to-purple-blue color change. In visible light, they can appear as red, yellow, dark blue, purple, green, or tan spots [20]. After spraying the vanillin sulfate reagent and then heating it. The above TLC results show a purple spot at RF 0.575, which is believed to be saponin glycosides at Rf 0.575.

Antidiabetic activity test

This test was conducted to determine the antidiabetic activity of the ethanol extract of Kabau leaves. The test was carried out on a diabetic animal model induced by alloxan at a dose of 120 mg/kg BW. The rats were acclimatized for 7 d in order for the rats to adapt to the new environment by being given feed and drinking ad libitum.

In the test group, the normal control group was used as a comparison for all test groups to determine the physiology of normal mice, while the negative control group was used as a comparison against other groups to see the occurrence of hyperglycemic conditions without being given antidiabetic drugs. The positive control group was used as a comparison against the test extract group and the dose groups I, II, and III were used to see the activity of the extract in lowering blood glucose levels in rats.

The formation of a diabetic animal model was assessed from fasting blood glucose levels 150 mg/dl and showed a typical condition or symptom of diabetes in rats[22], namely polyuria which was indicated by a higher amount of husk weight, and polydipsia from the amount of drinking intake compared to normal controls. Polydipsia is a condition where you feel constantly thirsty. While polyuria is a condition where there is abnormal urine production and these symptoms can occur together with polydipsia [23-25].

The experimental rats used in this study experienced polydipsia and polyuria; this was indicated by the higher amount of drinking intake and total husk weight in the treatment groups than the normal group.

Table 4: The results of measuring blood glucose levels after diabetes induction and after treatment in each test group

Test group	Blood sugar levels 7 d after alloxan induction, (mg/dl)±SD (n = 5)	Blood sugar levels after 14 d treatment with test substances, (mg/dl)±SD (n = 5)
Normal Control	121.33±5.51^{bcdef}	119.00±6.56^{bef}
Negative Control	375.67±17.50^{ad}	526.67±8.509^{acdef}
Positif Control (Glibenclamide 0.45 mg/kg p.o.)	351.00±13.23^{ad}	122.33±2.52^{bef}
Kabau leaf ethanol extract 250 mg/kg p.o.	429.67±41.43^{abcef}	129.67±4.73^{bef}
Kabau leaf ethanol extract 500 mg/kg p.o.	356.67±33.47^{ad}	78.67±13.32^{abcdf}
Kabau leaf ethanol extract 1000 mg/kg	346.33±20.98^{ad}	52.33±14.57^{abcde}

Values represent mean±SD, n=5, a = significantly different with normal control ($p<0.05$), b = significantly different with negative control ($p<0.05$), c = significantly different with the positive control (Glibenclamide 0.45 mg/kg p. o) ($p<0.05$), d = significantly different with Kabau leaf ethanol extract 250 mg/kg p. o ($p<0.05$), e = significantly different with Kabau leaf ethanol extract 500 mg/kg p. o ($p<0.05$), f = significantly different with Kabau leaf ethanol extract 1000 mg/kg p. o ($p<0.05$)

Based on table 4 shows that the administration of a single dose of alloxan 120 mg/kg via the intra-peritoneal route is able to induce diabetes. Test animals in all test groups experienced hyperglycemia (>126 mg/dl) or a significant increase in blood glucose levels compared to test animals in the normal control group. The increase in glucose levels due to alloxan induction in all groups of test animals was relatively the same statistically except for the 250 mg/kg Kabau extract group, which experienced the highest hyperglycemia condition compared to other groups of test animals. However, this study was still included in the study because it was included in the criteria for an animal model of diabetes.

Typical symptoms of diabetes were also observed in the negative control group who had polyuria and polydipsia. The total weight of the husks was heavier than the normal control group because it was very wet with the urine of rats with polyuria and polydipsia, as shown in fig. 2.

Based on table 4, the administration of ethanol extract of Kabau leaves for 7 d in a diabetic rat model showed hypoglycemic activity. Blood glucose levels decreased significantly in test animals to reach levels below 126 mg/dl. The pattern of pharmacological activity is dose-dependent; the larger the dose given, the greater the activity.

The mechanism of hypoglycemic activity of Kabau leaf ethanol extract that occurs is probably due to its ability to stimulate insulin secretion. This is evidenced in the diabetic animals that form type 2 diabetes with relative insulin deficiency, where the test animals are still able to secrete insulin when stimulated by either the drug glibenclamide or ethanol extract of Kabau leaves so that blood glucose levels drop significantly.

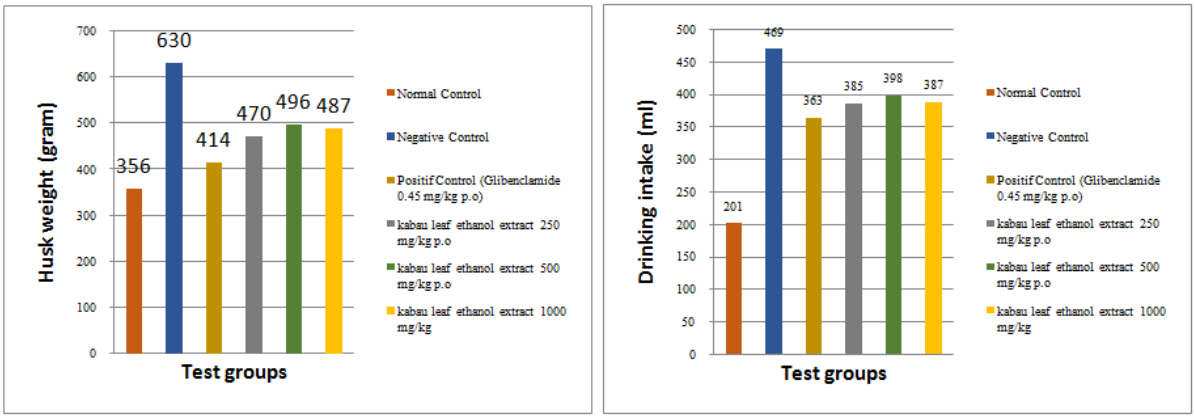


Fig. 2: Graph of the results of observing the condition of polyuria through the weight of husks and polydipsia through the amount of drinking per day

Based on fig. 2, the administration of ethanol extract of Kabau leaves at all doses showed that the test animals had improved symptoms of diabetes, namely polyuria and polydipsia, which were assessed from the lighter weight of the husks and the smaller amount of drinking intake in the test animals compared to the negative control group. Improvement of these symptoms in which a decrease in blood glucose levels is thought to come from secondary metabolites, based on the results of TLC by spraying specific chromogenic reagents for the secondary metabolite compound group indicated the presence of flavonoid compounds, phenolics, terpenoids, and saponins. Flavonoids and phenols can be antidiabetic because flavonoids are able to act as compounds that can neutralize free radicals so as to prevent damage to pancreatic beta cells that produce insulin [24]. Flavonoids and phenolic groups are reported to have antidiabetic activity by inhibiting amylase and increasing glucose absorption through sodium glucose transporter (S-GLUT) in cells. Likewise, isoflavones, tannins, and saponins have a mechanism of action by inhibiting the sodium-glucose transporter [25] S-GLUT is controlled by the hormone insulin, which is secreted by pancreatic cells in response to increased blood glucose levels. In diabetes mellitus, S-GLUT in skeletal muscle, heart muscle, and adipose tissue will decrease, resulting in a decrease in glucose absorption by cells, which increases blood glucose levels [26].

Measurement of MDA (Malondialdehyde)

The results showed that the administration of alloxan caused an increase in MDA levels, which can be seen in table 5. The negative control group had the highest MDA levels, which was significantly different from the other groups. Under normal circumstances, free radicals are formed in the body very slowly and slowly. When free radicals increase beyond the endogenous defense capacity, there will be an imbalance between the number of free radicals and endogenous antioxidants, resulting in oxidative stress. Oxidative stress causes excessive lipid peroxidation. The result of lipid peroxidation is MDA, so increased lipid peroxidation can cause MDA levels in the body to increase [27].

Table 5: Results of average levels of MDA

Group	Average levels of MDA (µl/ml)±SD (n = 5)
Normal Control	0.018±0.001
Negatif Control	0.105±0.008
Positif Control	0.046±0.003
Dose 1	0.042±0.001
Dose II	0.036±0.002
Dose III	0.024±0.003

Values represent mean±SD, n=5

The results of the spectrophotometer showed a significant difference between doses 1, 2, and 3 compared with positive control and negative control. Dosage 1 resulted in an average MDA level of 0.042, dose 2 0.036, and dose 3 0.024 it showed that there was free radical-reducing activity from Kabau leaf extract, where it was compared to the negative control, whose average MDA level was 0.105. These results are good because the average value is below the positive control, which is 0.046. The smaller the average value, the better the antioxidant activity. Of the three doses, the one that gave the best antioxidant activity was dose 3, with an average of 0.024, which was close to the normal control value with an average MDA value of 0.018. The greater the dose given, the greater the antioxidant activity. The antioxidant activity of the extract is influenced by the secondary metabolites contained in the extract, the results of qualitative analysis of TLC using chromogenic reagents in the extract are suspected to contain terpenoids, saponins, phenolics, and flavonoids. Flavonoids can act as antioxidants by capturing free radicals by giving hydrogen atoms to these radicals. The ability of flavonoids to scavenge DPPH radicals.

These flavonoid phenoxy radicals are stabilized by the delocalization of unpaired electrons around the aromatic ring. The stability of flavonoid phenoxy radicals (RO.) will reduce the speed of propagation (propagation) of chain reaction autoxidation.

Flavonoids are polyphenolic compounds (containing several phenolic hydroxyl groups) and several other compounds. It is this chemical property that underlies the many impressive *in vitro* pharmacological effects of this compound. In particular, flavonoids can complex with metal ions, act as antioxidants, and bind to proteins such as enzymes and structural proteins (this last feature may also explain flavonoids' ability to enhance connective tissue's ability). The antioxidant properties of flavonoids *in vitro* have been the main focus of most studies in recent years. Flavonoids can be complex with metal ions such as iron that may add to their antioxidant effect in these special circumstances. Most notable is the ability of flavonoids to inhibit macrophage-assisted oxidation of LDL, thereby promoting atherogenesis. The antioxidant properties of flavonoids may also contribute to their anti-inflammatory and antiplatelet effects and are attributed not only to their structural properties but also their ability to interact and penetrate the lipid layer of cell membranes. Flavonoids scavenge nitric oxide radicals, superoxide anions, and singlet oxygen. Like most other antioxidants, flavonoids can also act like pro-oxidants under certain conditions [28].

The presence of tannins also affects antioxidant activity. In contrast to flavonoids, tannins are a class of polyphenolic compounds that are also commonly found in plants. Tannins can be defined as polyphenolic compounds with a very large molecular weight of more than 1000 g/mol and can form complex compounds with proteins. The structure of the tannin compound consists of a benzene ring (C6) bonded to a hydroxyl group (-OH). Tannins have a great biological role because of their function as protein precipitates and metal chelators. Therefore, tannin is predicted to act as a biological antioxidant [29-31].

Most antioxidant studies on flavonoids have concluded that an ortho-dihydroxy (catechol) structure in B is important for high scavenging activity. Antioxidant activity is highly dependent on the presence of hydroxyl groups and also the number and configuration of OH groups present in a molecule [32, 33]. It also depends on the donation of hydrogen atoms. The terpenoid group of compounds works by donating hydrogen atoms so that it inhibits the occurrence of lipid peroxidation (LPO), which has the potential as free radicals [34]. Several monoterpenes can facilitate glucose uptake via upregulation of the glucose transporter (GLUT4) translocation, enhance insulin signaling pathway, promote insulin secretion, protect pancreatic cells and ameliorate proinflammatory cytokines [35].

CONCLUSION

Based on the research that has been done, it can be concluded that: Ethanol extract of Kabau leaves (*Archidendron bubalinum)* can reduce blood glucose levels in male white rats of Wistar strain after being induced by alloxan a dose of 1000 mg/kg BW can reduce high blood glucose levels by 33%. Based on the results of one-way ANOVA ($p<0.05$) the dose was 1000 mg/kg body weight and Measurement of MDA levels in test animals given a dose of 1000 mg/kg BW gave a value of 0.024±0.003.

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AUTHORS CONTRIBUTIONS

All the authors contributed equally.

CONFLICT OF INTERESTS

Declared none

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