



# Exploration of the Potential of Dandang Gendis Leaf Extract (*Clinacanthus nutans* L) as an In Vitro Antidiabetic (A-Glucosidase Enzyme Inhibition Test) and In Vivo (Decrease Glucose Levels and Glut-2 Expression in Mice)

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**Abstract.** Diabetes mellitus is thought to play a role in increasing free radicals, de-creasing antioxidants and triggering oxidative stress, and causing damage to GLUT 2. GLUT 2 on the pancreatic cell membrane is responsible for the transport of blood sugar in mice which will stimulate insulin secretion. Dandang gendis (*Clinacanthus nutans* L) leaves have the potential as antidiabetic because of the flavonoid compounds that function as antioxidants. Antioxidants are compounds that can reduce the negative impact of oxidants in inhibiting. Dandang gendis leaf extract (DGLE) was obtained by maceration extracting dandang gendis leaves. Methods. In vitro  $\alpha$ -glucosidase enzyme inhibition test and in vivo test of blood sugar (glucose) levels and Glut-2 expression in mice. Research result in the  $\alpha$ -glucosidase enzyme inhibition test gave an IC<sub>50</sub> value of 7.27 ppm and was active as an antidiabetic. There was a difference in the effect of giving on reducing blood sugar levels in mice, with the optimal concentration of DGLE 100 mg/kgBW which has activity in reducing blood sugar levels in mice by 51.60%. There was an increase in Glut-2 expression on DGLE distribution. Conclusion DGLE has the potential as an antidiabetic with the mechanism of inhibition of the  $\alpha$ -glucosidase enzyme, decreasing blood sugar levels and increasing Glut-2 expression.

**Keywords:** Antidiabetic ·  $\alpha$ -Glucosidase · Dandang Gendis Leaves

## 1 Introduction

Diabetes mellitus is a serious chronic disease caused by the failure of the pancreas to produce enough insulin (a hormone that regulates blood sugar in mice) and is an important public health problem, becoming a major public health problem. of the four non-communicable diseases are prioritized for authority. Follow up [1]. GLUT-2 or glucose transporter 2 is a protein carrier that facilitates glucose to cross cell membranes and has low affinity found in the intestine, liver, kidney, pancreatic  $\beta$ -cells, neurons, and in the system central nervous system. GLUT-2 in pancreatic cells is required glucose for insulin secretion [2]. GLUT-2 works to catch a signal when there is an increase in the level of blood glucose in the body, plays a role in responding to elevated glucose levels by the ability of pancreatic cells to secrete insulin and postprandial glucose uptake in the intestines and liver [3]. Based on the data and information center of the Ministry of Health of the Republic of Indonesia in 2018, Indonesia is ranked 4th among the 20 countries with the highest estimated number of diabetes cases in 2020 and 2030. [1]. These problems encourage the search for antidiabetic drugs from natural ingredients that are more effective and have minimal side effects by using ethnopharmaceutical and ethnobotanical approaches [1]. Previous research reported that one of the plants that have a high content of antioxidant compounds is dandang gendis, so it becomes an attraction for researchers in searching for antidiabetic phytopharmaceuticals [4]. Dandang gendis leaf ethanol extract which is the best extract has been tested to contain antioxidants such as flavonoids, saponins, and tannins reported to have antidiabetic properties [5].

Diabetes mellitus can cause oxidative stress so that free radicals in the body increase. Free radicals or ROS (reactive oxygen species) can damage various body tissues. The state of hyperglycemia in DM triggers the autoxidation of blood sugar which produces ROS [6]. In research that has been reported using experimental animals by providing ROS-producing agents such as Streptozotocin and alloxan, the production of ROS is not matched by the production of antioxidants so pancreatic  $\beta$  cells die. Previous studies have shown that the level of GLUT 2 protein expression decreases (down-regulation) in pancreatic  $\beta$  cells due to the induction of streptozotocin nicotine amide which causes toxicity to pancreatic  $\beta$  cells so that they are damaged and decrease insulin secretion and increases blood sugar levels of blood mice where the percentage density is brown. GLUT 2 protein in the induction rat group the result was 32.31%, while in normal controls the brown color density of high GLUT 2 protein was considered 100% [7]. ROS in the body must be balanced so that antioxidants are needed to combat excessive ROS. Streptozotocin (STZ) and alloxan are chemicals that are often used to induce experimental animals to become diabetes mellitus [8].

Alloxan can cause insulin-dependent diabetes mellitus in experimental animals. This substance is selectively toxic to pancreatic  $\beta$  cells that produce insulin due to the accumulation of alloxan specifically through GLUT 2. The mechanism of alloxan that can cause diabetes is that alloxan has a molecular shape similar to the blood sugar of mice (glucomimetic), so when alloxan is induced into the body of mice, GLUT 2 present in pancreatic  $\beta$  cells will recognize alloxan as blood sugar of mice, and alloxan is transported to the cytosol. In the cytosol, alloxan will undergo a redox reaction that produces ROS. The formation of ROS will lead to  $\beta$  cell membrane depolarization and increase  $Ca^{2+}$ , so the cytoplasm will activate different enzymes that cause lipid

peroxidation, DNA fragmentation, and protein fragmentation leading to pancreatic beta cell necrosis. Their insulin synthesis is reduced and decreased excretion [9].

Antioxidants are compounds that can reduce or inactivate ROS attacks, which are the result of chemical reactions and metabolic processes that occur in the body [10]. Various scientific evidence shows that antioxidant compounds reduce the risk of chronic diseases, such as cancer and heart disease.

## 2 Materials and Methods

### 2.1 Material and Tools

The materials used in this study were dandang gendis leaves obtained from the Health Polytechnic of the Ministry of Health Makassar and ethyl acetate p.a,  $\alpha$ -glucosidase enzyme, p-nitrophenyl- $\alpha$ -D-glucosidase (p-NPG), phosphate buffer, Na<sub>2</sub>CO<sub>3</sub>, aquabides, DMSO, quercetin, mice, alloxan, glibenclamide, primary antibodies. Anti-GLUT 2 mouse, alcohol (70%, 80%, 90%, 95%), H<sub>2</sub>O<sub>2</sub>, methanol, phosphate-buffered saline (PBS), BSA, DAB, and xylol. The tools used in research photometer, analytical balance (Sartorius), micropipette (Ependorf), a set of minor surgical instruments, histopathological examination tool for routine staining Haemo-toxyllin Eosin, a set of maceration apparatus, a set of rotary evaporator (Buchi), magnetic stirrer, UV-Vis spectrophotometer (Hewlett Packard), weighing scale animals, syringe centrifuge, oral needle, binocular microscope, camera and mouse cage.

### 2.2 Methods

The research methods include maceration using organic solvents as well as in vitro antidiabetic testing with  $\alpha$ -glucosidase enzyme inhibition methods and in vivo testing with diabetes mellitus mouse models.

**$\alpha$ -Glucosidase Enzyme Inhibition Activity Test.** Testing of  $\alpha$ -glucosidase enzyme inhibition activity followed the procedure in Table 1. The sample concentrations used were 15 ppm, 30 ppm, 60 ppm, and 90 ppm. Meanwhile, for the positive control used quercetin which was dissolved at concentrations of 0.65 ppm, 1.25 ppm, 2.50 ppm, and 5.00 ppm. The working procedure of the  $\alpha$ -glucosidase inhibition reaction can be seen in Table 1. The working procedure was carried out four times with four different concentrations for samples and controls [11].

**Test Blood Sugar Levels in Mice.** This research was conducted with the recommendation of research ethics approval from the Health Polytechnic of the Ministry of Health Makassar Number: 0626/KEPK-PTMKS/X/2021. The study used 24 mice (*Mus musculus*) which were divided into 6 groups, namely the MH group (healthy control = 1% w/v Na CMC), MS group (negative control = sick control = 50 mg/kgBW alloxan induction), the M50 group (induction of alloxan 50 mg/kgBW + 50 mg/kgBW), the M100 group (induction of alloxan 50 mg/kgBW + 100 mg/kgBW), the M150 group (induction of alloxan 50 mg/kgBW + 150 mg/kgBW) and the MG group (positive control = induction of alloxan 50 mg/kgBW + glibenclamide 0.65 mg/kgBW) [12].

**Table 1.**  $\alpha$ -glucosidase inhibition reaction procedure [11].

	Blank	Blank Control	Comparison	Comparison Control	Sample	Sample Control
Sample ( $\mu$ L)	-	-	5	5	5	5
DMSO ( $\mu$ L)	5	5	-	-	-	-
Buffer ( $\mu$ L)	450	450	450	450	450	450
Substrate ( $\mu$ L)	250	250	250	250	250	250
Incubation at 37 <sup>0</sup> C for 5 min						
Buffer ( $\mu$ L)	-	250	-	250	-	250
Enzyme ( $\mu$ L)	250	-	250	-	250	-
Incubation at 37 <sup>0</sup> C for 5 min						
Na <sub>2</sub> CO <sub>3</sub> ( $\mu$ L)	1000	1000	1000	1000	1000	1000
Measured absorbance at $\lambda = 400$ mm						

**Analysis of the Effect of Mice Treatment on the Development of Mice's Body Weight.** The body weight of mice for the MH, MS, M50, M100, M150, and MG groups was weighed for 14 days.

**Glut-2 Expression Analysis in Mice Group (MH, MS, M50, M100, M150, and MG).** Immunohistochemistry (IHC) procedure was performed in three steps, namely (1) preparation of slides for pancreatic tissue samples (2) optimization of dilution and activity time of anti-GLUT antibodies -2 (3) immunohistochemistry (IHC) on samples, light microscopy and semi-quantitative densities of GLUT-2 protein expression [7].

### 3 Results

#### 3.1 $\alpha$ -Glucosidase Enzyme Inhibition Activity

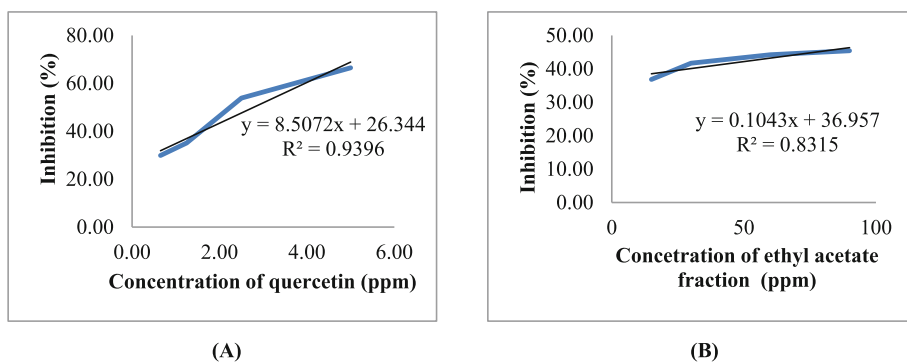
The  $\alpha$ -glucosidase activity inhibition test from DGLE aims to determine the potency of the extract used as antidiabetic based on the IC<sub>50</sub> value. In this study, DGLE was chosen as a sample because empirically *Clinacanthus nutans* L leaves are believed to be able to treat diabetes mellitus (DM).

In this study using quercetin as a control, quercetin is a flavonoid compound that has an inhibitory effect such as acarbose. Results of Inhibition of  $\alpha$ -Glucosidase Enzyme Activity by Control and Extraction can be seen in Table 2 and Fig. 1.

**Table 2.** Result of Inhibition of  $\alpha$ -Glucosidase Enzyme Activity by Control and Extraction

No	Test Material	IC <sub>50</sub> (ppm)
1	Ethyl acetate fraction	7.28
2	Quercetin	2.78

Source: Primary Data 2021



**Fig. 1.** (A) Graph of the relationship between the percentage of  $\alpha$ -glucosidase enzyme inhibition and quercetin concentration (B) Graph of the relationship between the percentage of  $\alpha$ -glucosidase enzyme inhibition between the concentration of ethyl acetate

### 3.2 The Average Blood Sugar Levels of Mice Blood Mice that were Induced by Alloxan During Treatment

The average blood sugar levels of mice in the MH, MS, M50, M100, M150, and MG groups can be seen on the histogram which can be seen in Fig. 2.

Figure 2's Description :

MH = Healthy control group.

MS = Negative control = pain control = alloxan induction 50 mg/kgBW.

M50 = Alloxan induction 50 mg/kgBW + 50 mg/kgBW.

M100 = Induction of alloxan 50 mg/kgBW + 100 mg/kgBW.

M150 = Alloxan induction 50 mg/kgBW + 150 mg/kgBW.

MG = Positive control = induction of alloxan 50 mg/kgBW + glibenclamide 0.65 mg/kgBW.

H0 = blood sugar levels of mice on day zero (before alloxan induction).

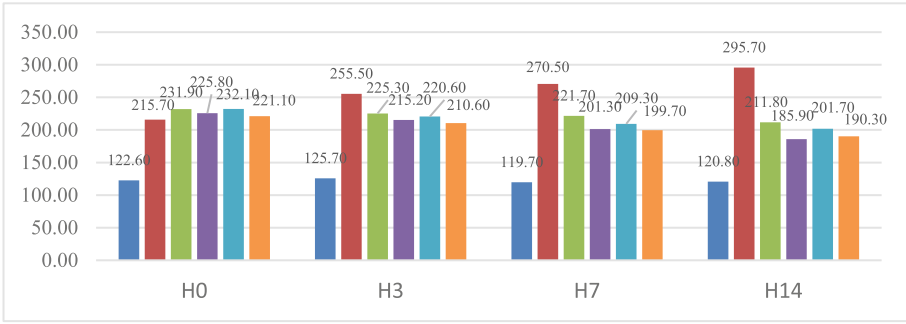
H3 = blood sugar levels of mice after 3 days of alloxan induction.

H7 = blood sugar levels of mice after 7 days of alloxan induction.

H14 = blood sugar levels of mice after 14 days of alloxan induction.

The results of the percentage reduction in blood sugar levels of mice in the MH, MS, M50, M100, M150, and MG groups can be seen in Table 3, then continued in the form of a histogram which can be seen in Fig. 3.

Result of Glut-2 Expression Analysis in Mice Group (MH, MS, M50, M100, M150, and MG).

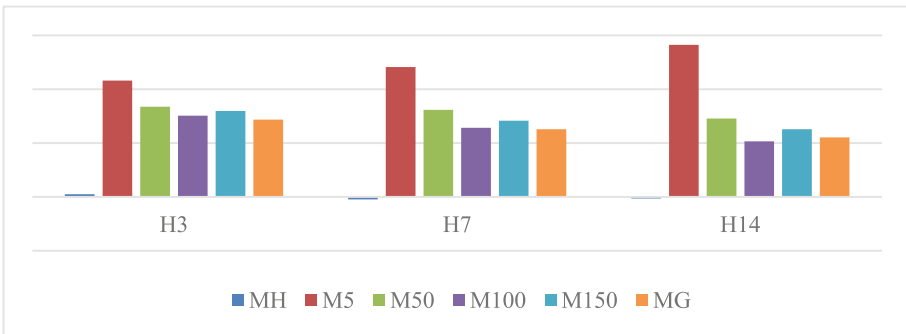


Note : MH (NaCMC) MS (Alloxan) M50 (CN50)  
 M100 (CN100) M150 (CN 150) MG (Glibenclamide)

**Fig. 2.** Average blood sugar levels of mice blood on days 0, 3, 7, and 14 (Source: Primary data, 2022)

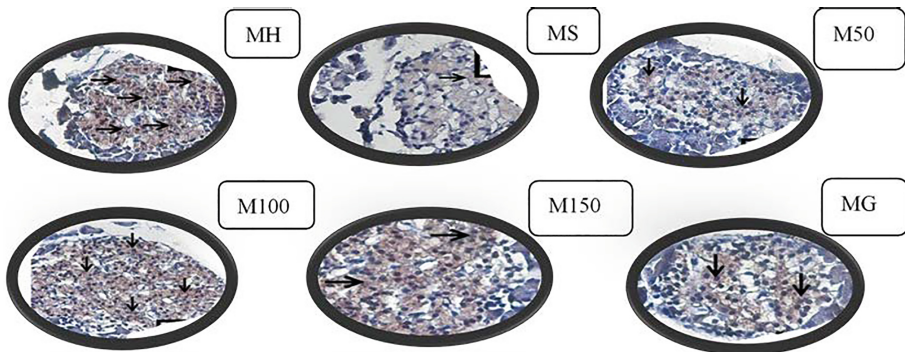
**Table 3.** Results of the Percentage of Decrease in Blood Sugar of Mice Induced by Alloxan after Treatment [13]

Observation	Treatment					
	MH	M5	M50	M100	M150	MG
H3	2.5%	108%	83.8%	75.5%	79.9%	71.8%
H7	2.4%	120.6%	80.8%	64.2%	70.7%	62.9%
H14	1.5%	141.2%	72.8%	51.6%	62.9%	55.2%



**Fig. 3.** Percentage of decrease in blood sugar levels in mice blood on days 3, 7, and 14.

The results of GLUT-2 expression in mice can be seen in Fig. 4.



**Fig. 4.** IHC GLUT – 2 staining results in a group of mice. Arrow indicating the presence of GLUT – 2 expressions indicated by the presence of brown color.

## 4 Discussion

### 4.1 DGLE Potential Against $\alpha$ -glucosidase Enzyme Inhibitory Activity

The  $\alpha$ -glucosidase activity inhibition test from DGLE aims to determine the potency of the extract used as an antidiabetic based on the IC<sub>50</sub> value. In this study, dandang gendis leaves were selected as samples because the empirical dandang gendis leaves had believed to treat diabetes mellitus (DM) [12]. In this study using quercetin as a control, quercetin is a flavonoid compound that is able to inhibit the effect, such as acarbose [14].

The results of the calculation of the inhibitory activity of the  $\alpha$ -glucosidase enzyme in this study showed that each IC<sub>50</sub> value for quercetin was 2.78 ppm and DGLE ethyl acetate was 7.27 ppm. These results indicate the potential of DGLE as a very active antidiabetic according to the IC<sub>50</sub> value category range as Antidiabetic [11].

The immensity of the inhibitory ability of the  $\alpha$ -glucosidase enzyme shown by several medicinal plants is different from one another. The difference occurs caused by several factors, including differences in the content of secondary metabolites in a plant and the type of solvent used in the extraction [11]. That is by research [15] has that the aqueous extract of the yellow wood root has an IC<sub>50</sub> value of 48.68632 g/mL, and ethanol extract from the yellow wood root has an IC<sub>50</sub> value of 66.9616 g/mL, which is the difference in the number of the enzyme inhibitory activity of  $\alpha$ -glucosidase between aqueous and ethanol extracts in the yellow wood root (kayu kuning) cannot be separated from the content of secondary metabolites contained in each plant and the type of extraction solvent used.

The significant difference in the inhibition value is strongly influenced by the chemical structure of a compound. The position and number of hydroxyl (OH) in the flavonoid molecule is the determining factor of enzyme inhibition, the more hydroxyl groups will increase the inhibitory activity. Quercetin has five hydroxyls (poly hydroxyl) groups that interact with the active site of the enzyme. Interactions may occur in the inhibition process, where the 3-OH substitution will form hydrogen bonds with the active site Asp349 of the active site of the  $\alpha$ -glucosidase enzyme, while the catechol part of ring B forms

**Table 4.** Results of statistical analysis of reducing blood sugar levels in mice

Descriptive	N	Percentage of decrease in blood sugar levels of blood mice (mg/dL)					
		Treatment Group					
		MH	MS	M50	M100	M150	MG
Mean	4	-0,46	123,26	79,13	63,77	71,16	63,3
SD	4	2,60	16,76	5,69	11,96	8,51	8,31
Median	4	-1,5	120,6	80,8	64,2	70,7	62,9
Min	4	-2,4	108	72,8	51,6	62,9	55,2
Max	4	2,5	141	83,8	75,5	79,9	71,8

hydrogen bonds with the active site of Asp68, Asp214, and Glu276 of the -enzyme  $\alpha$ -glucosidase. In addition, the -OH group at C-3 functions to maintain proper binding to flavonoid molecules [15]. Another interaction is the occurrence of a conjugate system in the quercetin ring structure  $\alpha$ -glucosidase enzymes hydrolyze alpha ( $\alpha$ ) glycosidic bonds located between sugar residues. By inhibiting the action of the  $\alpha$ -glucosidase enzyme, it causes a decrease in monosaccharide absorption and a reduction in the increase in blood sugar in postprandial mice.

**4.2 Potential of DGLE Against Blood Sugar Levels Reduction of Blood Mice**

Data analysis in Table 4 shows that the DGLE intervention in the M100, M150, and MG groups affected the decrease in blood sugar levels of mice induced with alloxan and for the M50 group had no effect on reducing blood sugar levels in mice that were induced with alloxan. This is because DGLE and glibenclamide can suppress the increase in blood sugar levels of blood mice by activating pancreatic cells for insulin production.

**4.3 Effect of DGLE on Changes in Body Weight of Mice During Treatment**

The occurrence of weight loss in mice in the MS-positive diabetes mellitus group was caused because the mice with diabetes mellitus were unable to use the mice’s blood

**Table 5.** Results of statistical analysis of changes in body weight of mice

Descriptive	N	change in weight of mice (g)					
		Treatment Group					
		MH	MS	M50	M100	M150	MG
Mean	4	35.03	27.23	30.39	32.24	30.92	30.77
SD	4	1.25	5.55	1.92	0.861	0.41	0.74
Median	4	35.15	27.70	30.21	32.49	30.85	30.67
Min	4	33.52	20.75	28.3	31.01	30.52	30
Max	4	36.32	32.76	32.86	32.97	31.48	31.76



sugar as an energy source, this was due to a lack of insulin. Although insulin hormone measurements were not carried out, theoretically it can be confirmed that the mice with diabetes mellitus in this study were insulin deficient because alloxan induction damaged insulin-producing pancreatic beta cells [8]. Lack of insulin causes the mice's blood sugar cannot enter the cells so that the energy needs for the body are obtained from lipolysis. Fat in various tissues is mobilized and degraded through the beta-oxidation process to produce energy. Loss of fat causes the mice to lose weight. The same thing was also reported by [16], who stated that weight loss in mice is one of the characteristics of alloxan-induced diabetes mellitus. Changes in the body weight of mice varied after experiencing diabetes mellitus. For people with diabetes mellitus, although the blood sugar levels of mice are high, the cells cannot utilize the blood sugar or liver through the process of gluconeogenesis so this situation causes the mice to lose weight. On the 7th day, 14th day to 21st day, the ethanol extract of white flesh dragon fruit (*Hyllocereus undatus*) 2% at a dose of 50 mg/kgBW, a dose of 100 mg/kgBW, and glibenclamide at a dose of 65 mg/kgBW. There was an increase in the average body weight of mice. This is because the ethanol extract of dragon fruit and glibenclamide has been able to suppress the increase in blood sugar levels in mice by activating pancreatic beta cells for insulin production. So, insulin becomes normal and cells get enough energy. This causes the mice's blood sugar to be stored properly in the muscles and liver so that the mice's body weight gradually increases (Table 5).

DGLE Potential in Enhancing GLUT-2 Expression GLUT-2 in healthy mice functions to transport blood sugar in mice and functions in the process of insulin secretion in the body to stabilize the regulation of blood sugar in mice [3]. Alloxan induction in mice can cause damage to pancreatic cells and cause insulin secretion to decrease [17], so they are unable to transmit signals to attract GLUT-2 to the active site on the cell membrane and resulting in decreased GLUT-2 activity [18]. GLUT-2 remains in the cell membrane but cannot be active because there is high oxidative stress which causes islet cell damage, thus interfering with insulin secretion and resulting in the mice's blood sugar being unable to be metabolized, resulting in hyperglycemia. Alloxan enters the pancreatic  $\beta$  cells through GLUT-2 which is present in the plasma membrane.

The distribution of antioxidants can reduce oxidative stress in diabetes mellitus I. The distribution of antioxidants and polyphenolic compounds can capture free radicals and reduce oxidative stress [19]. The distribution of therapy containing antioxidants can increase the expression of GLUT 2. The content of flavonoid compounds acts as an antioxidant capable of neutralizing free radicals. Antioxidants can neutralize free radicals by complementing the electron deficiency of free radicals thereby inhibiting the occurrence of oxidative stress. Giving therapy containing antioxidants to DM mice was able to inhibit the destruction of pancreatic  $\beta$  cells by neutralizing free radicals. Furthermore, cells can regenerate cells so that there is an increase in the number of cells and can increase the production of insulin synthesis which is used to transmit signals to attract GLUT 2 to the active site on the cell membrane [3].

## 5 Conclusion

The  $\alpha$ -glucosidase enzyme inhibition test of DGLE ethyl acetate gave an IC<sub>50</sub> value of 7.27 ppm and was active as an antidiabetic. Giving DGLE ethyl acetate of 100 mg/kgBW, it is active in reducing blood sugar levels in mice by 51.6%. The distribution of DGLE ethyl acetate fraction was able to increase the expression of GLUT-2 in mice with an alloxan-induced diabetes mellitus model at a dose of 100 mg/kgBW.

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