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By Dora Dayu Rahma Turista Qurrotu 'yunin Lathifah

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In Vivo Antidiabetic Properties of *Etlingera elatior* Leaf Extract in Alloxan-Induced Diabetic Rats

Dora Dayu Rahma Turista[1]*, Qurrotu A'yunin Lathifah[2], Arif Nur Muhammad Ansori[3], Yulanda Antonius[4], Gabrielle Ann Villar Posa[5], Wahyu Choirur Rizky[6], Tim Godefridus Antonius Dings[7], Galiya Kazhibayeva[8], Karina Omarova[8], Irina Anikina[8]

[1]Educational Biology Department, Faculty of Teacher Training and Education, Mulawarman University, Samarinda, Indonesia.
[2]Department of Medical Laboratory Technology, STIKES Hutama Abdi Husada, Tulungagung, Indonesia.
[3]Doctoral Program in Veterinary Science, Faculty of Veterinary Medicine, Universitas Airlangga, Surabaya, Indonesia.
[4]Faculty of Biotechnology, University of Surabaya, Surabaya, Indonesia.
[5]School of Environmental Science and Management, University of the Philippines Los Baños, Los Baños, Philipines.
[6]College of Medicine, Sulaiman Al Rajhi University, Al Bukayriyah, Qassim, Saudi Arabia.
[7]College of Medicine, Maastricht University, Maastricht, The Netherlands.
[8]Department of Biotechnology, Toraighyrov University, Pavlodar, Kazakhstan.

*Corresponding author:
Educational Biology Department,
Faculty of Teacher Training and Education,
Mulawarman University,
Samarinda, East Borneo 75119, Indonesia
E-mail address: doraturistaofficial@gmail.com
Tel: +6285730477725

ABSTRACT:
Diabetes mellitus is a metabolic disease characterized by hyperglycemia. Application of alloxan in experimental animals can cause Diabetes mellitus. The secondary metabolites of *Etlingera elatior* can be used as raw materials for diabetes mellitus drug. This study aims to determine the antidiabetic potential of ethanol extract of *Etlingera elatior* leaves by *in vivo* study. A total of 32 rats were divided into 6 groups, namely NC, DC, PC, DE1, DE2, and DE3. The results of data analysis using multivariate ANOVA on blood glucose level data every week showed p (0.000) < (0.05), and the results of data analysis using one way ANOVA on pancreatic β cell count data also showed that p (0.000) < (0.05). *Etlingera elatior* leaf ethanol extract has antidiabetic activity since it could reduce blood glucose levels and increase the number of pancreatic β cells through several mechanisms. The mechanism is triggered by phytochemical compounds contained in the leaf extract of *Etlingera elatior*.

KEYWORDS: Alloxan, diabetes mellitus, *Etlingera elatior,* blood glucose level, pancreatic β cells

INTRODUCTION:

Diabetes mellitus is metabolic diseases that is characterized mainly by hyperglycemia which caused by defect of insulin secretion, action of insulin, or both. Chronic hyperglycemia in diabetes result a long-term complication[1]. This disease is related to obesity, hypertension, and abnormal lipid profile, such as high triglyceride levels, low of high-density lipoprotein (HDL), high total cholesterol[2] and increases the risk of cardiovascular diseases[3,4]. People with diabetes mellitus reached 422 million worldwide and caused 1.6 million deaths each year[5]. The morbidity rate of diabetes continuously rising until now. The world has agreed that it will stop the increase in the number of diabetes cases by 2025[5].

According to American Diabetic Association (ADA, 2021) Diabetes mellitus is divided into 3 types, namely type 1 diabetes mellitus (T1DM), type 2 diabetes mellitus (T2DM), and other specific types. T1DM is caused by destruction to the β-cells in the pancreas which cannot produce insulin optimally. It is either causing by immune-mediated process or idiopathic. Moreover, T2DM is caused by insulin resistance with relative insulin deficiency to a predominantly secretory defect. Other specific types of diabetes can be caused by genetic causes, diseased pancreatic exocrine, endocrinopathies, drug- or chemical-induced, or infections. Insulin regulates blood glucose levels by promoting glucose uptake from the blood to the cells. The pancreas is an organ that synthesizes and secretes the insulin, specifically by the β cells of the Langerhans islets. Insulin secreted by the pancreas into the portal vein then enters to the liver. Furthermore, it is distributed throughout the body through the blood circulation[5]. The disorders of the Langerhans islets cells have an impact on insulin secretion. When insulin secretion is impaired, the blood glucose increased, and it cannot even enter to the cells. Consequently, cells lack glucose as an energy-forming material.

Alloxan is a diabetogenic agent that commonly used to induce diabetes in experimental animals. It is an organic compound, urea derivative, and glucose analog which has carcinogenic and cytotoxic effect. It is chemically known as 5,5-dihydroxy pyrimidine-2,4,6-trione[6,7]. The use of alloxan in experimental animals can cause type 1 diabetes[8]. Alloxan works by inhibiting the glucokinase enzyme and inducing the formation of ROS. The glucokinase is a glucose sensor of beta cells. Furthermore, the inhibition of glucokinase inhibited the insulin secretion by β-cell, whereas ROS induce necrosis of β cells resulting in insulin-dependent diabetes[6]. During 15 hours after administration of alloxan at a dose of 170 and 200 mg/kg BW to the experimental animals showed several phases of glucose response were observed[8,9]. Intravenous alloxan-induced rats show biochemical changes in the blood[10].

Plants produced secondary metabolites that can be used as a raw material of drug[6], such as *Etlingera elatior*. The herbs medicines is commonly made from secondary metabolites and it showed various biological effects[11]. *E. elatior* contains a secondary compounds of alkaloids, terpenoids, steroids, saponins, and flavonoids[7]. Flavonoids and alkaloids can trigger the regeneration of pancreatic β-cells[8,9]. Flavonoids can also protect the pancreatic β-cells and help them to survive[12]. The flavonoids also act as antioxidants and it can increase insulin secretion[11]. Furthermore, it could repair the damaged pancreatic β-cells, and improve the insulin secretion. Therefore, the blood glucose level could be stable. This study aimed to determine antidiabetic potential of the ethanol extract of *Etlingera elatior* leaves by *in vivo* study. In brief, it could be determined through blood glucose levels and the number of pancreatic β cells in rats which injected by alloxan.

MATERIAL AND METHODS:

Material selection:

Alloxan monohydrate is procured from Merck (Sigma Aldrich). The standard drug Glibenclamide and Carboxymethylcellulose (CMC) were used as a negative control. Furthermore, the leaves of *Etlingera elatior* from Zingiberaceae family was used for the experiment. Furthermore, ethanol was selected as solvent for extraction.

Extract preparation:

The leaves of *Etlingera elatior* were washed, cut, and air-dried. The dried leaves was then processsed to be powder. Furthermore, 50 grams of *Etlingera elatior* powder was macerated with 250 mL of 96% ethanol for 48 hours at room temperature. Furthermore, solution of leaf extract was filtered and the filtrate was concentrated using a rotary evaporator[13].

Extract screening:

Screening of *Etlingera elatior* leaf extracts was conducted by following the Harbour Method[14]:

Flavonoids: 1 ml of concentrated extract was put into a test tube, about 1-2 ml of hot methanol was added, then the Mg metal powder was added. Furthermore, about 0.5 ml of concentrated HCl was added. If it produced a red or orange color, then the extract was positive for flavonoids.

Tannins: About 1.5 ml of concentrated extract was put into a test tube, then a few drops of hot distilled water were added. Moreover, it was cooled and filtered. Furthermore, three drops of 10% NaCl were filtered. Then two drops of $FeCl_3$ were added. If it produced a blackish green/dark blue color, then the sample was positive for tannins.

Saponin (forth method): One ml of concentrated extract was put into a reaction tube, then 5 ml of distilled water was added and shaken for 30 seconds. If it caused foam and did not disappear for 30 seconds, then the extract would be positive for saponins. However, to maintain the bias foam, 1 M HCl was added.

Phenolic: 1 ml of concentrated extract was put into a test tube, then 10 drops of 1% $FeCl_3$ were added. The extracts was considered contained of phenol if it produced green, red, purple, blue, or solid black color.

Alkaloids: 1 ml of concentrated extract was put into a test tube, then 3-5 drops of Dragendroff's reagent were added. The positive reaction occured when a brown or orange precipitate was formed.

Terpenoid/Steroid: 1 ml of concentrated extract was put into a test tube, then 0.5 ml of chloroform was added. Moreover, 0.5 ml of anhydrous acetate was added. The mixture was then added with 3-5 drops of concentrated H_2SO_4

through the wall. If a green or blue color was formed, then the extract was considered positive for steroids. Meanwhile, if a purple or brown ring was formed, the extract was determined as positive for triterpenoids.

Animal preparation:

This study was approved by the ethics committee for animal research at Faculty of Veterinary Medicine, Universitas Airlangga (2.KE.041.04.2020). In this study, the experimental were used male rats (*Rattus norwegicus*) with Wistar strain. Rats were at age 2-3 months and weighed about 175-200 grams with good health conditions.

Induction of diabetes mellitus:

The rats were acclimated in the laboratory for 7 days and ensured that their blood glucose levels were below 200 mg/dL before alloxan administration. White rats were induced to be diabetic by injecting a single dose of alloxan 175 mg/kg body weight (BW) intraperitoneally[15].

Experimental design:

The dose of *Etlingera elatior* leaf extract was using a human dose of 10 grams/50 kg BW or 14 grams/70 kg BW. Hence, it was converted into rats with weight 200 grams. In detail, it was calculated as follow: 0.018 x 14 grams = 0.252 grams or 252 mg. The *E. elatior* leaf extract was injected once a day according to the group dose with a treatment duration of 21 days. The determination of the number of rats was calculated using the Frederer formula. Total of 32 rats were divided into 6 groups, such as:

NC: Normal Control (treated with CMC in distilled water and non-alloxan-induced)
DC: Diabetes mellitus Control (CMC-treated in alloxan-induced)
PC: Positive Control (Glibenclamide-treated in alloxan-induced)
DE1: Diabetic Extract 1 (200 mg ethanol leaf extract/200 gram BW rats in alloxan-induced)
DE2: Diabetic Extract 2 (250 mg ethanol leaf extract/200 gram BW rats in alloxan-induced)
DE3: Diabetic Extract 3 (300 mg ethanol leaf extract/200 gram BW rats in alloxan-induced)

Research data collection:

Blood glucose levels were measured every 7 days, i.e. days 0, 7, 14, 21, and 28 after treatment. Blood was taken from the tail and it was examined by using a glucometer. The examination of pancreatic cell structure was carried out 28 days after treatment. The rats were dissected and their pancreas was taken for histopathological preparations by using the Hematoxylin Eosin (HE) staining method. After staining, the preparations were examined using a microscope with a magnification of 400× within 5 fields of view.

Data analysis:

Data analysis using the IDB SPSS software (version 20). Weekly blood glucose levels were analyzed by multivariate ANOVA and the number of pancreatic β-cells were analyzed by one way ANOVA. Furthermore, the post hoc was analyzed by using the LSD test. The P-value was <0.05 ($p<0.05$) based on statistical significance.

RESULTS AND DISCUSSION:

Plants contain a phytochemical compounds which resulted from secondary metabolism. The results of a qualitative screening of the phytochemical content of the *Etlingera elatior* leaf ethanol extract is presented in Table 1.

Table 1. Phytochemical content of *Etlingera elatior* leaves ethanol extract

Phytochemicals	*Etlingera elatior* Leaf
Flavonoid	+
Tannin	+
Saponin	+
Phenolic	+
Alkaloid	+
Triterpenoid	+
Steroid	-

This experiment was conducted after the rats blood glucose levels reached above 200 mg/dL due to alloxan induction. In general, this study resulted in two data which are presented in the form of mean, namely blood glucose levels every week from week 0 to week 4. Moreover, the number of pancreatic β-cells after the rats were dissected at week 4. Blood glucose levels per week are presented in Figure 1 and the number of pancreatic β cells are presented in Figure 2.

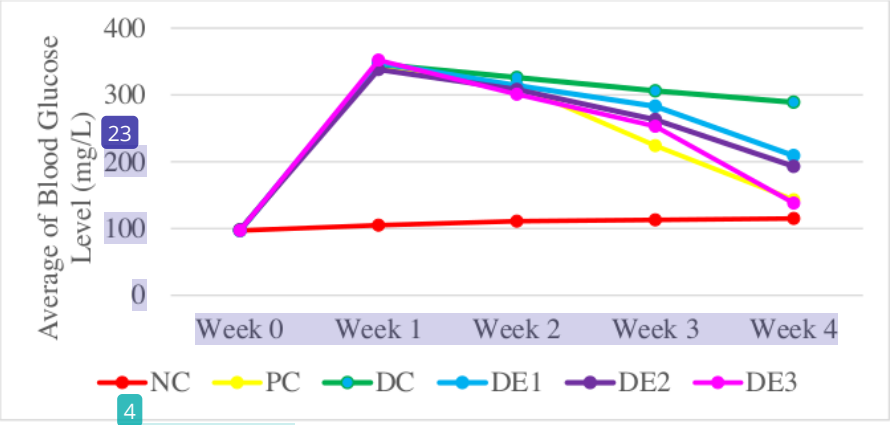

Figure 1. Rats Blood Glucose Levels

The data of rats' blood glucose levels in every week were carried out by comparative analysis using multivariate ANOVA and it was found that p (0.000) < (0.05). Furthermore, the LSD test was carried out and it was found that at week 4, there was no significant difference observed for DE3 as compared to NC (p=0.054) and PC (p=0.607).

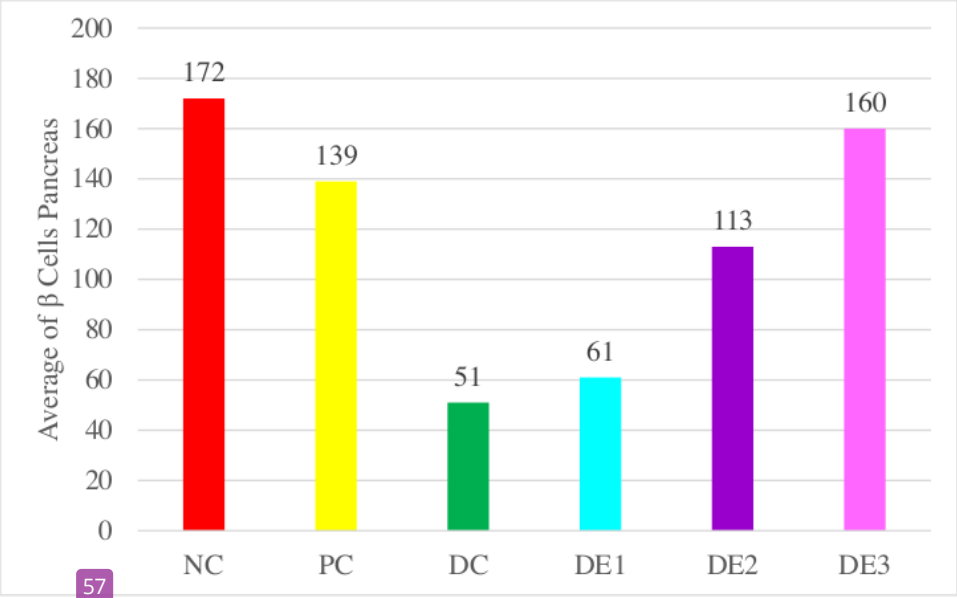

Figure 2. The Number of Rat Pancreatic Beta Cells

The data on the number of pancreatic β cells in rats was carried out by a comparative analysis using one way ANOVA and the results showed a significant difference between groups (p<0.05). Furthermore, the LSD test was carried out and it was found that DE3 showed no difference to NC (p: 0.580) and PC (p: 0.307).

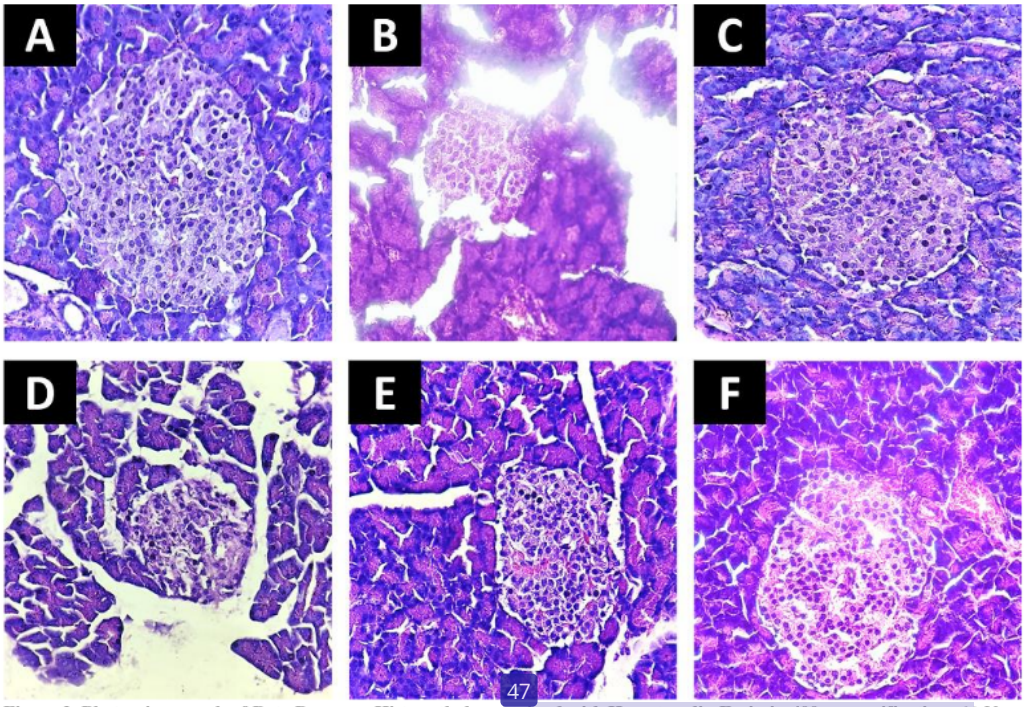

Figure 3. Photomicrograph of Rats Pancreas Histopathology stained with Hematoxylin Eosin in 400× magnification: A) Normal Control: Normal rats that given CMC, B) Diabetes mellitus Control: Diabetes mellitus rats that just given CMC, C) Positive Control: Diabetes mellitus rats that given Glibenclamide, D) Diabetic Extract 1: Diabetes mellitus Rats that given 200 mg ethanol leaf extract/200 gram BW rats, E) Diabetic Extract 2: Diabetes mellitus Rats that given 250 mg ethanol leaf extract/200 gram BW rats, F) Diabetic Extract 3: Diabetes mellitus Rats that given 300 mg ethanol leaf extract/200 gram BW rats.

Figure 3A is histopathology of the pancreas of normal rats without alloxan induction. It showed that the islets of Langerhans are in good condition with a large number of β-cells without damage observed. Figure 3B is the histopathology of diabetes mellitus rats due to alloxan induction and without therapy. It appeared that the islets of Langerhans are damaged, the boundaries of the islets are not clear, and the β-cells are few due to necrosis or apoptosis. Figure 3C is the histopathology of the diabetic rats' pancreas that was treated with glibenclamide for 4 weeks, it appears that the islets of Langerhans are good with a large number of β cells and there is no damage to β cells. Whilst, figure 3D is the histopathology of the diabetic rats' pancreas that was treated with 200 mg ethanol leaf extract/200 gram BW rats, it shows that islets of Langerhans are damaged and the β cells are few due to necrosis or apoptosis. Figure 3E is the histopathology of the diabetic rats' pancreas that was treated with 250 mg ethanol leaf extract/200 gram BW rats. It showed that the number of β cells are increased. Figure 3F is the histopathology of the diabetic rats' pancreas that was treated with 300 mg ethanol leaf extract/200 gram BW rats. It shows the best results with good Langerhans islets and the number of β cells under conditions similar to those of normal mouse pancreas and glibenclamide-treated rats' pancreas.

The blood glucose level of rats increased above the normal limit (200 mg/dL) after alloxan administration with a single dose of 175 mg/200g BW (Figure 1). This is because alloxan is a toxic substance that can cause damage to pancreatic β-cells. Alloxan is a highly toxic compound and it is commonly used to induce diabetes mellitus in animals. In brief, it works in two ways, such as causing insulin dependence and causing necrosis of pancreatic β-cells[6]. Alloxan induced partial degradation of pancreatic cells so that the quality and quantity of insulin are impaired[8]. Insulin synthesis begins with the formation of preproinsulin and it is processed into proinsulin and subsequently converted into insulin and C-peptide is stored in secretory granules and secreted on demand[16].

Blood glucose level in diabetes mellitus rats is related to the condition and number of β-cells in the Langerhans islets. In normal rats, the pancreas appeared normal with large islets of Langerhans without any damage to β-cells (Figure 1a) and a high number of β-cells (Figure 2). The size of the pancreatic Langerhans islets in diabetic rats is also smaller and many of their β-cells are damaged (Figure 3b). Furthermore, the number of β-cells decreased (Figure 2). Islets consisting mostly of only remnants of α and β cells show decreased in the islet size, β granules, and granular endoplasmic reticulum[17]. This is due to the pathological effect of the alloxan.

Alloxan is very harmful to pancreatic β-cells which is insulin-producing cells but it is not harmful to α cells as glucagon-producing cells[15]. The alloxan is selectively absorbed very quickly by pancreatic β cells since it has similarities to glucose in molecular form and hydrophilicity, thus eventually accumulates in the cells[8]. The transport of alloxan into the cytosol of β-cells is also similar to that of glucose, namely through facilitated diffusion by glucose transport protein 2 (GLUT2). The GLUT2 transporter is usually located on the plasma membrane of β-cells.

Alloxan is a highly unstable compound and it is susceptible to a redox reaction[8]. It caused diabetes through the inactivation of essential sulfhydryl enzymes which is involve the combination of essential sulfhydryl groups and oxidized to disulfide bonds and vice versa[18]. Alloxan reduction produces dialuric acid which is further oxidized by alloxan and the same step is continuously repeated. The autoxidation of dialuric acid is believed to be very important in the diabetogenic action of alloxan because it formed intracellular reactive oxygen species (ROS), such as hydroxyl radicals and superoxide radical anions that can trigger the tissue damage[19]. This reaction will occur in cycle and continue when there are intracellular thiols, especially glutathione (GSH)[8].

Alloxan induces ROS activation which is a common mediator of necrotic cell death. The β-cells are highly susceptible to ROS. It will inhibit insulin or insulin-like growth factor (IGF)-1, insulin receptor (IR), insulin receptor substrate (IRS) -1, and phosphatidylinositol-3 kinase (PI3K)/Akt kinase. Furthermore, it induced the β-cell damage, decrease insulin secretion and led to diabetes[20]. ROS caused mitochondrial injury, cell membrane damage, disturbing ion balance through protein damage, lipid peroxidation, and oxidative DNA damage[21–23]. Furthermore, ROS are associated with oxidative stress that causes damage to lipids, proteins, and DNA[24,25] which resulting in apoptosis cell[26,27]. In addition to necrosis, the dead β-cell is also caused by apoptosis, so that the number of β-cells decreased[28–30]. Necrosis can induce the release of inflammatory cytokines, such as IL-1, IL-4, IL-13, and other inflammatory mediators. Whereas apoptosis can lead to the release of anti-inflammatory cytokines including TGF-β and IL-10[31]. Moreover, oxidative stress can cause diabetes-related cell and tissue damage[32,33].

Administration of ethanol extract of *Etlingera elatior* leaves could reduce the blood glucose levels of diabetic rats (Figure 1). During 200 mg/200 g BW, the treatment showed that blood glucose levels decreased but it did not reach the normal levels. The dose of 250 mg/200 g BW showed the decrease of normal blood glucose levels (>200 mg/dL) after week-4. The decreased of maximum blood glucose level was found in the diabetic rats treated with 300 mg/200 g BW of extract. In addition, it demonstrated the highest level in this study. This is consistent with the results of the data analysis which showed the effect of blood glucose reduction in the diabetic rats. This effect is considered as dose-dependent. However, treatment with 300 mg/200 g BW is also showed that the state of the Langerhans islets is looked substantial (Figure 3d) with number of beta cells close to non-diabetic rats (Figure 2). This condition is related to the phytochemical content of extract. Treatment with higher dose increased the levels of phytochemicals absorbed by the rat's body.

Etlingera elatior leaf ethanol extract contains of compounds, such as flavonoids, tannins, saponins, phenolics, alkaloids, and triterpenoids (Table 1). The flavonoids are phenolic compounds resulting from secondary plant metabolism which are classified into subclasses flavonols, flavanones, flavones, isoflavones, flavonols, anthocyanidins, and flavanonols[12,34,35]. Flavonoids can prevent the diabetes and its complications[36,37]. Flavonoids can strengthen the capacity of insulin secretion and the process of β-cell survival through the antioxidant and antidiabetic activities[37].

Tannins are polyphenolic biomolecules that had high molecular weight and widely distributed in various plant species[38]. In detail, it divided into two groups, such as hydrolyzed tannins (molecules with polyhydroxy components) and thick tannins (formed from the condensation of flavanols)[38,39]. Tannins also had an antidiabetic activity by inhibiting the activity of α-amylase[40] and α-glucosidase enzymes[41].

Saponins are secondary metabolites of amphipathic glycosides which are synthesized by various plant species and it has high molecular weights. Moreover, it consists of a sugar moieties, such as glucose, galactose, glucuronic acid, xylose, rhamnose or methylpentose, glycosides linked to the hydrophobic aglycones (sapogenins) which may be triterpenoids or steroids[42,43]. Saponins with one sugar group are called monodesmosidic, but saponin with two sugar groups are called bidesmosidic[44]. Saponins have been reported to stimulate insulin release, blocking the formation of glucose in the bloodstream[45], having mild inhibition of α-amylase enzymes and inhibition of strong against the enzyme glucosidase[46].

Alkaloids are derived from natural sources which contained of nitrogen atoms in heterocyclic compounds. Furthermore, it has various types of ring structures[45,47]. Furthermore, alkaloids also have hypoglycemic activity[48]. The biomolecule is believed to have anti-diabetic properties since it can overcome the insulin resistance, reduce blood glucose levels, and accelerate the β-cell rejuvenation in diabetic experimental animals[49].

Triterpenes are produced by plants and marine animals which are formed through the composition of squalene epoxide followed by condensation, esters or glycosides (saponins) form in free condition[45,50]. Triterpenes are believed to have antidiabetic activity and inhibit diabetes the complications[51,52]. It involves in several signaling mechanisms including

activation of insulin signaling pathways, inhibition of PTP1B, GP, 11β-HSD1, α-glucosidase, α-amylase, and activation of AMPK and PPAR[51].

Various results *in vitro* and *in vivo* showed that flavonoids[32,53–59], tannins[60–62], saponins[63–68], phenolics[69–75], alkaloids[76–81], and triterpenoids[51,52,76,82–89] are phytochemical compound that have antioxidant activity. The endogenous and exogenous antioxidants had an essential role in cell defense mechanisms. It protects and repairs the cell damage by inhibiting the ROS production and scavenging free radicals[32,33,90]. Exogenous antioxidants derived from natural ingredients strengthen the endogenous antioxidant defenses[91,92]. The increased levels of antioxidants in the body could protect against degenerative diseases[39,92].

The pancreas has a low levels of antioxidants. Therefore, *Etlingera elatior* leaf extract is considered to increase the antioxidant capacity through Nrf2 activation. Phytochemicals can activate Nrf2, thereby increasing antioxidant response and preventing β-cell death[93]. Previous studies shown that the ethanol extract of *Centipeda minima*[94], with aqua extracts of *Polygonatum sibiricum*[95], and ethanol extract of *Sargassum horneri* (Turner) C. Agardh[96], could also activate the Nrf2 signaling pathway. Moreover, the Nuclear factor erythroid 2-related factor 2 (Nrf2) is a transcription factor that manage the cellular defense against toxic and oxidative attacks through the gene's expression in oxidative stress response and drugs detoxification[97]. When the cells are exposed to oxidative stress or electrophilic compounds, the Nrf2 will dissociates from Keap1 and enters the nucleus to bind antioxidant-responsive elements in genes encoding antioxidant enzymes[98].

Blood glucose levels are also related to the condition and number of pancreatic β-cells. Furthermore, accurate respond to the blood glucose levels with a sufficient number of β-cells are required[99,100]. The recent study revealed that insulin-producing cells in mice could be regenerated[101].

The administration of *Etlingera elatior* leaf extract stimulates the β-cells regeneration, so that the number of β-cells increased. The regeneration potential of β-cells is very limited in the absence of external stimuli, but in the presence of external stimuli there is a sufficiently strong regenerative the β-cell mass expansion resulting from the activation of inactivated precursors/progenitors or stem cells[102].

Etlingera elatior leaves have the potential to be used as herbal medicines for diabetes mellitus treatment because they have antidiabetic properties, and it is easy to obtain. Several phytochemicals from medicinal plants have been developed as new types of diabetes mellitus therapy[89]. Plants are a source of natural antioxidants and effective herbal medicines related to its anti-diabetic compounds, such as flavonoids, tannins, phenolics, and alkaloids. These compounds enhanced the pancreatic tissue performance by increasing insulin secretion or decreasing the glucose absorption in the intestine[79]. Moreover, the phytotherapy is excellent since it is safe, cheap, and abundantly available in nature. However, further research is needed to determine the mechanism of action and the molecular interactions of compounds within the body.

CONCLUSION:

Etlingera elatior leaf ethanol extract was able to significantly reducing the blood glucose levels and increasing the number of pancreatic β-cells. The *Etlingera elatior* leaf is considered as a potential candidate for antidiabetic mellitus drug since it is determined as safe, cheap, and easy to obtain. However, further research is needed to determine the mechanism of action and the molecular interaction of the compounds within the body.

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CONFLICT OF INTEREST:

The authors declare no conflict of interest.

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