ANTIHIPERGLICEMIC ACTIVITY OF ETHANOL EXTRACT OF JUMPAI BATANG (Glinus oppositifolius (L.) Aug. DC.) IN OVERLOADED SUCROSE-SWISS STRAIN MALE MICE

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Introduction

There were 425 million people with diabetes mellitus (DM) worldwide in 2017. [1]. Indonesia ranks sixth after China, India and the United States, Brazil, and Mexico, with an estimated 10.3 million people with DM. Basic Health Research report [2] showed that the prevalence of DM in Indonesia based on diagnosis or symptoms was 2.1%. Antidiabetic drugs usually last for a long time with significant side effects. (3)Diabetes mellitus is a group of metabolic diseases characterized by hyperglycemia and impaired carbohydrate, fat, and protein metabolism associated with an absolute or relative deficiency of the action and secretion of insulin by pancreatic β-cells [3],[4]. Type-1 diabetes mellitus results from destroying pancreatic beta cells due to an autoimmune process. However, in a minority of patients, there is no evidence of autoimmunity, or it is idiopathic. Generally, clinical symptoms occur when the destruction of pancreatic cells reaches ≥90%. Type 2 diabetes mellitus is a hyperglycemic disease due to cellular insensitivity to insulin. Insulin levels may be slightly decreased or in the negative range.[5]

Oral antidiabetic drugs are part of the therapeutic management of diabetes if lifestyle modifications do not provide meaningful blood sugar reduction. According to the indication, patients are given oral hypoglycemic drugs (OHO) or insulin injections [6]. Several classes of oral hypoglycemic drugs (OHO), such as biguanides, sulfonylureas, thiazolidinedione (TZD), DPP-4 inhibitors, SGLT-2 inhibitors, glinides, α-glucosidase inhibitors, and GLP-1 receptor agonists [6]. But the administration of synthetic drugs can provide several side effects, including weight gain, hypoglycemia, dyspepsia, diarrhoea, lactic acidosis, oedema, and urinary tract infection. Therefore, alternative treatment with low side effects and efficacy that is not much different from synthetic drugs is needed. One alternative is the use of traditional medicine from natural ingredients [7]. One of the plants that have the effect of lowering blood sugar is Jumpai Plant (Glinus oppositifolius (L.) Aug. DC). [8], [9].

The Jumpai plant (Glinus oppositifolius (L.) Aug. DC.) is native to tropical and subtropical regions. In Indonesia, this plant is a weed. By the surrounding community, jumpai plants are believed to cure symptoms of appendicitis, accelerate wound healing, increase appetite and reduce blood sugar levels, that this plant is also widely used to fight various types of diseases related to immune response, intestinal infections, joint pain, inflammation, fever, malaria and wounds. [9] As a traditional medicine, the jumpai plant contains glycosides, flavonoids, phenols, steroids, saponins and alkaloids [10]. And phenolic compounds from their biological effects as antimicrobial, antioxidant, anti-inflammatory, and anticancer. (From several previous studies, ethanol extract of the jumpai plant (Glinus oppositifolius (L.) Aug. DC.) has been reported as an antioxidant , anti-inflammatory, anticancer Astuti's research showed that ethanol extract of jumpai (Glinus oppositifolius (L.) Aug. DC.) is positive for flavonoid compounds and has potent antioxidant activity against DPPH with an IC50 value of 9,523 μg/mL.

Flavonoids in Jumpai (Glinus oppositifolius (L.) Aug. DC.) can increase insulin sensitivity by clearing insulin signalling pathways, activating insulin receptor tyrosine kinase, being able to inhibit the work of α-glucosidase enzymes that work by stimulating glucose in peripheral tissues and playing a role in enzyme expression through carbohydrate metabolic pathways. [11] In addition, flavonoids in Jumpai plants (Glinus oppositifolius (L.) Aug. DC.) [12] can also reduce the concentration of cholesterol in the blood so that it can reduce the incidence of diabetic complications so that the hypoglycemic effect can occur. Based on this background, the hypoglycemic test of ethanol jumpai (Glinus oppositifolius (L.) Aug. DC.) on male mice (Mus musculus) so that its use in society as a traditional medicine can be accounted.

Materials and methods

The tools used include aluminium foil, maceration vessel, porcelain cup, filter paper, Rotary evaporator, analytical balance, water bath, goblet, measuring flask 10 ml, 25 ml, 50 ml and 100 ml, glass beaker, Erlenmeyer, vial, micropipette, volume pipette, dropper pipette, analytical balance, horn spoon, and stirring rod.

The materials used include: ethanol extract of G. oppositifolius stem, 70% ethanol, methanol p.a, distilled water, aluminium chloride (Merck, Germany), gallic acid (Merck, Germany), citric acid (Merck, Germany), ethanol p.a (Merck, Germany), 70% ethanol, ethyl acetate (Merck,

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Germany), FeCl3 (Sigma-Aldrich), concentrated HCl (Merck, Germany), Quercetin (Sigma-Aldrich), n-Hexan (Merck, Germany), Na2CO3 7,5% (Merck, Germany), sodium chloride (Sigma-Aldrich), Mg powder (Sigma-Aldrich), Folin-Ciocalteau reagent (Merck, Germany), sodium acetate trihydrate, and TPTZ (Sigma-Aldrich).

Preparation of Simplisia and Powder of Jumpai Stem (Glinus oppositifolius (L.) Aug. DC).

The Jumpai (Glinus oppositifolius (L.) Aug. DC.) was cut first, spread on a tray, and then put into the oven to dry between 40-50^0 C for approximately 24 hours or until completely dry. After the simplicia is finished, then proceed with pollination using a pollinator. After the powder is completed, proceed with screening using sieve numbers 40 and 50 mesh.

Preparation of Jumpai Stem Extract (Glinus oppositifolius (L.) Aug. DC)

The dried simplicia was weighed and put into a maceration vessel. Then 70% ethanol solvent was added in a ratio of (1:10). Maceration was carried out three times 24 hours while stirring, then stored in a place not exposed to direct sunlight. The extract obtained was evaporated with a rotary evaporator until a thick extract was obtained.

Flavonoid Screening

A total of 200 mg of a sample extracted with 5 ml of ethanol is heated for 5 minutes in a test tube (making test solution), then a few drops of concentrated HCl are added, and 0.2 g of Mg powder is added. The onset

Preparation of 12% b/v Sucrose Solution

Sucrose used in inducing hyperglycemia is a concentration of 4 g/KBB. (16) The body weight is the average weight of mice, 30 g, and the maximum volume that can be given orally to mice is 1 mL. From the calculation results, the sucrose concentration given to mice is 12 grams/100 mL or 12% b/v.

Preparation of 1% Na CMC suspension

The 1% NaCMC suspension was made by dissolving 1 g of NaCMC into distilled water that had been heated at 70°C, then sufficient to 100 mL. Then stir until perfectly dispersed using an electric stirrer.

Preparation of acarbose suspension

The dose in adult humans is 50 mg (11), so the amount for 20 g mice is 0.0166 mg. They first weighed one by one acarbose tablets, as many as 30 tablets, and then calculated the average weight. The results were entered into the calculation formula: Weight of tablets weighed = (desired weight)/(etiquette weight) x average weight. Finely crushed 30 acarbose tablets, weighed 5.23 mg and put into a mortar, added 1% NaCMC suspension little by little while grinding until homogeneous and then put into a 25 mL flask. The volume is filled with 1% Na CMC suspension until the limit mark. (17).

Preparation of suspension of ethanol extract of stem (Glinus oppositifolius (L.) Aug. DC.)

The doses of extracts to be given are 100 mg/kg bb, 200 mg/kg bb and 400 mg/kg bb, so the doses for 20 g mice are 2 mg, 4 mg and 8 mg. Ethanol extract of the stem (Glinus oppositifolius (L.) Aug. DC.) weighed as much as 100 mg, 200 mg and 400 mg and then dispersed with 1% Na CMC until homogeneous. Then the volume is sufficient to 10 mL in a measuring flask (concentrations of 1%, 2% and 4%).

Test Animal Preparation

The test animals were male Swiss mice with a body weight of 20-30 grams, 2-3 months old, and in good health characterized by a healthy physical appearance and no defects, and moving actively. The test animals were first fed for 12 - 16 hours while still given a drink. The test animals are then adapted to the research environment for 18-24 hours. Determination of the number of test animals per group The calculation of the number of test animals used in the study was based on the analysis using the Federer formula, namely: (n-1) (t-1)≥15 In this study, the number of groups used was 5, so based on the Federer formula, the number of test animals used in each group was at least 4.
Which is,
n = Which is the number of test animals per group
t = number of test groups

Antihyperglycemic activity test

The test animals were randomly divided into five treatment groups, so the number of mice needed was 25. Group I is a negative control group (Na CMC), group II is an acarbose control group (positive control), and groups III, IV, and V are groups of ethanol extracts of jumpai plants (Glinus oppositifolius (L.) Aug. DC.) with three different doses of 75mg/kg bb, 150mg/kg bb and 300 mg/kg BB. After being fed, the treatment in group I was given 1% Na CMC, group II was given acarbose suspension at a dose of 80 mg/kg bb, and groups III, IV, and V were given ethanol extract of jumpai plant (Glinus oppositifolius (L.) Aug. DC.) with three different dose ratings and then waited for 30 minutes to reach onset. After 30 minutes, the blood sugar level of mice was

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measured as the 0th-minute blood sugar level in each group using a blood sugar checker (Accu check), where blood was taken from the lateral vein of mice. Then 12% sucrose induction was given to groups I-V. All treatments were carried out orally in mice. Furthermore, blood sugar levels were taken at 60, 120, and 180 minutes in each group. The levels obtained were then made into a graph of blood sugar levels versus time (minutes) 0 to 180 minutes using the trapezoidal method (AUCt0-tn). (18). The formula is as follows:

$$\mathbf{AUCt0-tn} = \frac{t1-t0}{2}\ x\ (\mathrm{C0}+\mathrm{C1}) + \frac{t2-t1}{2}\mathrm{x}C1+C2)+ \frac{\mathrm{tn}-\mathrm{tn}-1}{2}\ x\ (Cn-1+Cn)$$

t: time (minutes)
C: Blood sugar level (mg/dL)
$AUCt0$-in: the area under the curve from time 0 to time n
$AUCt0-$tn : the area under the curve from time 0 to time n

The formula for % reduction in blood sugar levels is as follows:

$$\%\ \mathrm{PKGO} = \frac{[1-\text{AUC perlakuan}-\text{AUC kontrol negatif}}{\text{AUC kontrol gula}-\text{AUC kontrol negatif}}\mathrm{x}\ 100\%$$

Data Collection and Data Analysis Techniques

Blood sugar data AUC0-180 were analyzed statistically, starting with determining whether the data obtained were negatively distributed or not through the Shapiro-Wilk test because of the number of samples <50 as a requirement for parametric analysis. If the data is negatively distributed, proceed with the Levene test to determine the variance and conduct a one-way variance pattern analysis (one-way ANOVA) with a confidence level of 95% and α = 0.05. If the data has the same variance, it is continued with the Bonferroni post hoc test. If the results show a P <0.05, then there is a significant difference in the mean between the two data groups; if there is a P>0.05, the difference in the mean is not meaningful. [13]

Results and discussion

This study aims to determine the effect of reducing blood sugar levels from the Jumpai Plant (Glinus oppositifolius (L.) Aug. DC). In this study, ethanol extract of the stem (Glinus oppositifolius (L.) Aug. DC.) from Wajo district, South Sulawesi Province, was determined at the Biology Laboratory of Makassar State University with reference number 029/SKAP/Lab. Biology/VII/2021. The determination results show that the plants used are Jumpai plants (Glinus oppositifolius (L.) Aug. DC).

In Nazia Hoque's study, it was reported that ethanol extract of the stem (Glinus oppositifolius (L.) Aug. DC.) has a large number of phenolic compounds, which act as antidiabetic compounds (8) because it can inhibit glucosidase resulting in a decrease in blood sugar concentration. Therefore, in this study, phytochemical tests were carried out to determine the compounds contained in the ethanol extract of the stem (Glinus oppositifolius (L.) Aug. DC). [14] In the results of phytochemical testing (table 1), positive results were obtained in the flavonoid compound test, so it can be concluded that the ethanol extract of the stem (Glinus oppositifolius (L.) Aug. DC.) contains flavonoid compounds.

Table I. Flavonoid Phytochemical Test Results of ethanol extract of stem (Glinus oppositifolius (L.) Aug. DC.)

Flavonoid test	Kualitative results
NaOH 10%	(+) brown
Magnesium+ HClp	(+) red
HCl Pekat	(+) red

M.N.F. Rizniya and Juliana Janet also reported the same results that the branch (Glinus oppositifolius (L.) Aug. DC.) contains many polyphenolic compounds in the form of flavonoids. M.N.F. Rizniya and Juliana Janet also reported the same results that the branch (Glinus oppositifolius (L.) Aug. DC.) contains many polyphenolic compounds in the form of flavonoids. These compounds are thought to be responsible for the effect of lowering blood sugar. In the study of the antihyperglycemic activity of ethanol extract of stems (Glinus oppositifolius (L.) Aug. DC.), 25 mice were randomly divided into five groups before treatment. The test animals were fed for 12-16 hours but still presented a drink so that blood sugar was stable and there were no changes in blood sugar levels due to food intake.

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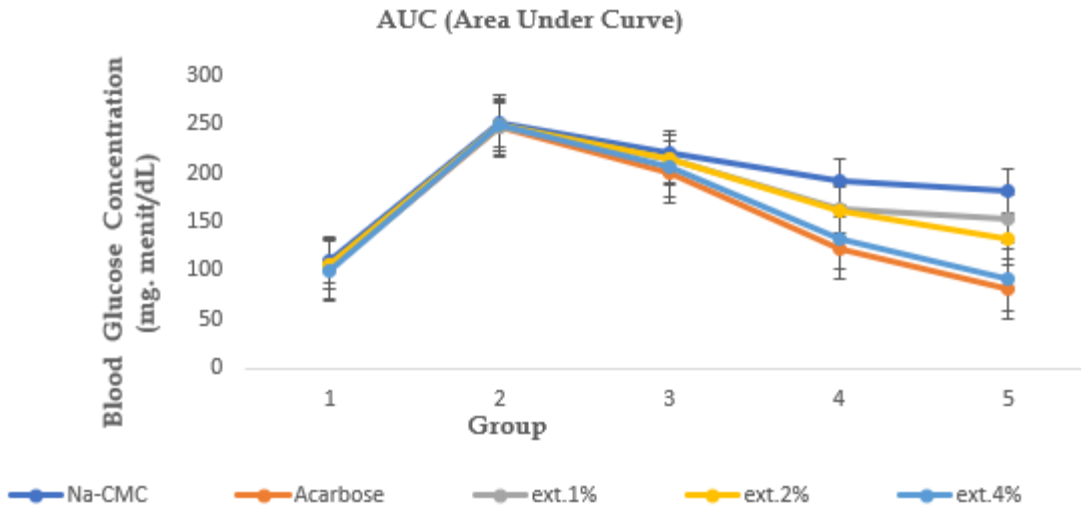

Figure 1: Relationship curve between time and mean AUC of blood sugar level

Table 2. Mean values of AUC0-180 from groups

Groups	**Mean values AUC0-180 (mg.menit/dL) ± SD**	**% PKGD**
Negative control	12590.00±77.10	-
Acarbose	9772.00±58.47	100.00
Cons. 1 %	11564.00±94.39	36.41
Cons. 2 %	11276.00±14.69	46.63
Cons. 4 %	10208.00± 32.86	84.53

Figure 1 above shows the profile of the increase in blood sugar in mice in each treatment group before and after being induced with sucrose; each control group experienced the highest growth in blood sugar at minute 0 after sucrose administration, then at minutes 60, 120, and 180 experienced a decrease in blood sugar while the negative group had no increase in blood sugar. According to the following research (22) that after giving blood sugar treatment will decrease at the 60th minute. The value of blood sugar levels obtained then calculated the value of the area under the curve (AUC) from minute 0 to minute 180 with the trapezoid method.
The administration of sucrose induces blood sugar levels in mice or creates a state of hyperglycemia. These results show that giving sucrose can increase blood sugar levels in mice.

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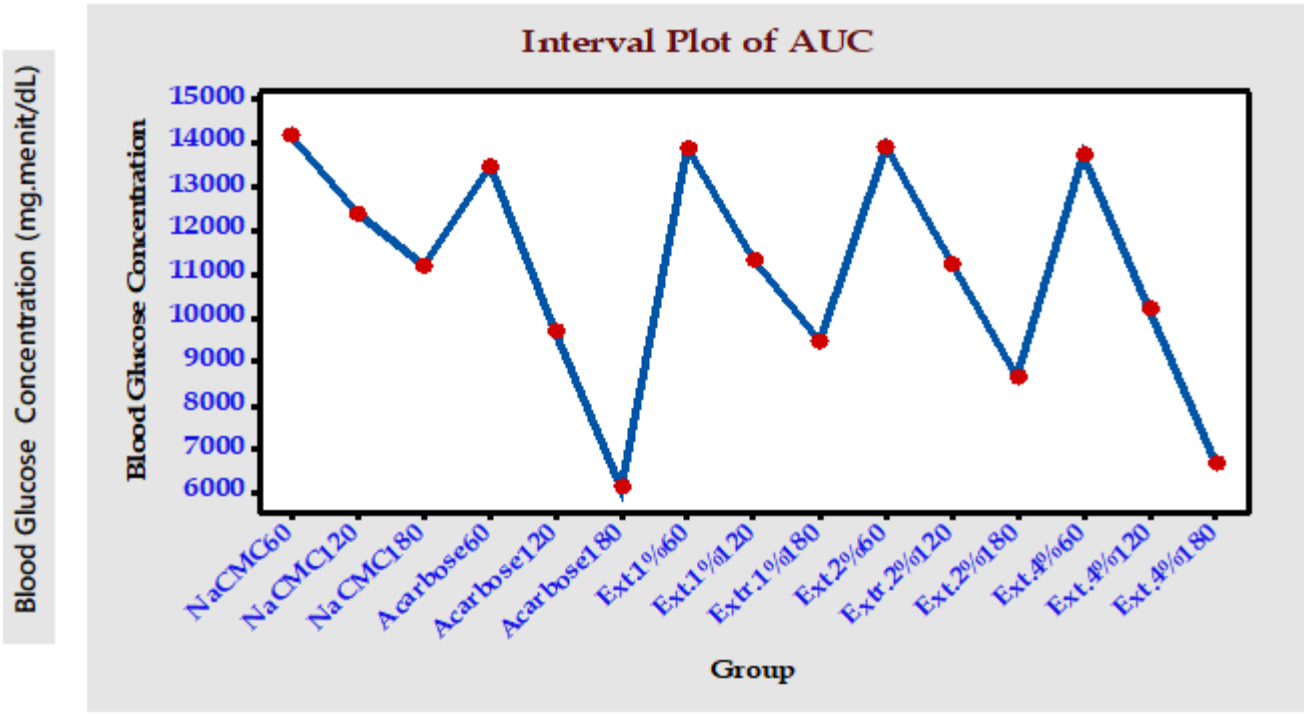

Figure 2. Bonferroni Post-Hoc Test Results AUC0-180 Blood Sugar Levels of Mice Sucrose Feeding

Control group acarbose

In this group, acarbose was given at 80 mg/kg bb. Acarbose is a competitive inhibitor of the α-glucosidase enzyme. It inhibits the enzyme's work in hydrolyzing saccharide complexes so that monosaccharides are produced in small amounts, absorption in the intestine decreases, and blood sugar levels do not increase drastically. (23) The mean AUC0-180 value is 9772 ± 58.470 mg.minute/dL In Figure 2 shows, the Bonferroni post-hoc test AUC0-180 blood sugar levels of mice acarbose control and negative control obtained a value of p = 0.000, indicating a significant difference. This result means that administering acarbose control can reduce blood sugar levels in male Swiss mice burdened with sucrose, with an average %PKGD of 100%. Statistical test results between acarbose control and negative control showed no significant difference, according to the following research (16) related to the effect of acarbose in reducing blood sugar levels in test animals that are orally burdened with sucrose.

Treatment Group ethanol extract of jumpai stem (Glinus oppositifolius (L.) Aug. DC)

This group was given three doses of ethanol extract of jumpai stem (Glinus oppositifolius (L.) Aug. DC.). The extract to be delivered is 100 mg/kg bb, 200 mg/kg bb and 400 mg/kg bb to know the effect of reducing blood sugar levels of male Swiss mice burdened with sucrose. The mean value of AUC0-180 and % PKGD, respectively, at a dose of 100 mg/kg bb is 11564 ± 94.394 mg. minute/dL and 36.408% when compared with the negative control group statistically obtained p=0.000, which means there is a significant difference between the treatment groups of 100 mg/kg bb dose. The mean AUC0-180 value of the 100 mg/kg bb dose compared to the acarbose control is p = 0.073, which means there is no statistically significant difference between the 100 mg/kg bb dose treatment group and the acarbose control group. From both statistical results, it can be concluded that the administration of ethanol extract of jumpai stem (Glinus oppositifolius (L.) Aug. DC.) at a dose of 100 mg/kg bb lowers blood sugar in mice.

The mean value of AUC0-180 and %PKGD, respectively, at a dose of 200 mg/kg bb is 11276 ± 14.696 mg. minute/dL and 46.628% when compared with the negative control group statistically obtained p=0.000, which means there is a significant difference between the 200 mg/kg bb dose treatment group and the negative control group. The mean AUC0-180 value of the 200 mg/kg bb dose compared to the acarbose group is p=0.335. There is no statistically significant difference between the 200 mg/kg bb dose treatment group and the acarbose control group. Based on the statistical results, it is known that the administration of ethanol extract of jumpai stem (Glinus oppositifolius (L.) Aug. DC.) dose of 200 mg/kg bb has a lowering effect on blood sugar in mice.

The mean value of AUC0-180 and % PKGD, respectively, at a dose of 400 mg/kg bb is 10208 ± 32.863

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mg. minute/dL and 84.528% when compared with the negative control group statistically obtained p=0.000, which means there is a significant difference between the treatment group dose of 400 mg/kg bb with the negative control group. The mean AUC0-180 value of the 400 mg/kg bb dose compared to the acarbose group is p=0.469. There is no statistically significant difference between the 400 mg/kg bb dose treatment group and the acarbose control group. The result shows a blood sugar lowering effect is due to the administration of ethanol extract of jumpai stem (Glinus oppositifolius (L.) Aug. DC.) dose of 400 mg/kg bb. The ability produced is almost the same as acarbose.

The study of the antihyperglycemic activity of ethanol extract of jumpai stem (Glinus oppositifolius (L.) Aug. DC.) was compared between treatment groups, namely ethanol extract of jumpai stem (Glinus oppositifolius (L.) Aug. DC.) with 100 mg/kg bb, 200 mg/kg bb dose, 400 mg/kg bb dose. The statistical analysis showed the comparison between ethanol extract of jumpai stem (Glinus oppositifolius (L.) Aug. DC.) 100 mg/kg bb and 200 mg/KGB obtained p = 1, which means that there are differences that are not statistically significant. This shows that a 100 mg/kg bb dose provides a blood sugar-lowering effect equivalent to 200 mg/kg bb.

Comparison between ethanol extract of jumpai stem (Glinus oppositifolius (L.) Aug. DC.) doses of 100 mg/kg bb and 200 mg/kg bb gave a value of p = 1, which means that there is no statistically significant difference between the two ethanol extracts of jumpai stems (Glinus oppositifolius (L.) Aug. DC). This means that the dose of 200 mg/kg bb reduces blood sugar levels relatively the same as that of 100 mg/kg bb with a value of p = 1.

In the study of the antihyperglycemic activity of ethanol extract of jumpai stem (Glinus oppositifolius (L.) Aug. DC.), the dose of 400 mg/kg bb is an effective concentration because when compared with the negative control, it produces a p=0.000 value, which means that there is no statistically significant difference between the 400 mg/kg bb dose treatment and the negative control. This result follows the operational definition of effective concentration: the treatment that provides a significant difference against the acarbose control, and the difference is not significant against the negative control. The % PKGD of the 400 mg/kg bb dose is 84.528% higher than other concentrations and is also close to the %PKGD of acarbose 80 mg/kg bb dose, which is 100%.

Phytochemical screening showed that ethanol extract of Glinus oppositifolius (L.) Aug. DC.) has phenolic content that affects an antihyperglycemic. The higher the concentration, the antihyperglycemic effect will decrease as the concentration increases. This is attributed to the nature of some phenolic compounds that can inhibit insulin release at high concentrations. There is also a decrease or even loss of activity of the extract components at high concentrations. [15]. There is also the possibility of saturation and an increase in concentration. In this case, there is an equilibrium between the solute and the solvent phase, which results in the diffusion process not going well. According to Suman Pattanayak, flavonoids contained in ethanol extract of the stem (Glinus oppositifolius (L.) Aug. DC.) can increase insulin sensitivity by clearing the insulin signalling pathway which has the potential to activate the insulin receptor tyrosine kinase in the insulin signalling process.

Conclusion

The results prove that the ethanol extract of the stem (Glinus oppositifolius (L.) Aug. DC.) lowers blood sugar levels of sucrose-loaded Swiss Galu male mice. The effective dose of ethanol extract of Glinus oppositifolius (L.) Aug. DC.) is at 400 mg/kg bb with AUC0-180 of 10208 ± 32.863 and % PKGD of 84.528%.

Antihiperglicemic activity of ethanol extract of Jumpai batang (Glinus oppositifolius (L.) Aug. DC.) in overloaded sucrose-swiss strain male mice

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Background: Diabetes mellitus is a metabolic disorder associated with relative or absolute insulin deficiency or resistance, characterized by hyperglycemia. Modern prescriptions such as pioglitazone have better therapeutic potential. However, the side effects and financial burden for developing countries have motivated researchers to find alternative natural drugs to compete with hyperglycemia in diabetic patients. This study was conducted to explore the therapeutic potential of selected medicinal plants for treating diabetes as an alternative to allopathic drugs. (Glinus oppositifolius (L.) Aug. DC. is one of the alternative natural ingredients with high flavonoid compounds with hyperglycemia activity. The purpose of this study was to determine the effect of reducing blood sugar levels of ethanol extract of jumpai stem (Glinus oppositifolius (L.) Aug. DC.)) in male Swiss mice that are burdened with sucrose and the effective concentration of blood sugar levels. **Methods:** The type of research used in this study is pure experimental complete randomized design unidirectional pattern. A total of 25 mice were randomly divided into five groups, namely the negative control group, positive control (acarbose 80 mg/KgBB), sucrose control, and treatment concentration rating of ethanol extract of jumpai stem (Glinus oppositifolius (L.) Aug. DC.), namely 5%; 10%; and 15% orally. Sucrose was given 30 minutes after treatment. Observations were made at 0, 60, 120, and 180 minutes after sucrose was given by taking blood from the tail. Analysis of results using the trapezoidal method

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(AUC t0- tn) and statistical analysis using Shapiro-Wilk, Levene test, one-way ANOVA, and post-hoc Bonferroni. **Results:** It has been investigated that treatment of sucrose-induced diabetic mice with ethanol extracts of the stems of the studied medicinal plants showed a significant effect (P <.05) on fasting blood glucose levels (from baseline to normal range) in a manner comparable to that of reference drugs. The tested plant extracts significantly (P <.05) reduced the glucose concentration in the blood of diabetes-induced mice dose-dependently. The results showed that ethanol extract of jumpai stem (Glinus oppositifolius (L.) Aug. DC.) reduced blood sugar levels in sucrose-loaded male Swiss mice. The effective concentration of blood sugar level reduction of ethanol extract of jumpai stem (Glinus oppositifolius (L.) Aug. DC.) is 4%. **Conclusion:** It can be concluded that the studied medicinal plants have antihyperglycemic activity. The findings of this study support the use of traditional herbal medicine practices for managing diabetes, which may be due to the presence of bioactive phytoconstituents in the plants.

Keywords: Diabetes Mellitus, Antihyperglycemic, Jumpai (Glinus oppositifolius (L.) Aug. DC.)

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