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Potential of Therapeutic *Curculigo latifolia* Extracts on Alloxan-induced Diabetes in a Male *Mus muscullus*

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Abstract. *Curculigo latifolia* is a herbaceous plant that is abundant on the islands of Java, Sumatra and Kalimantan. C. *latifolia* has not been well explored. The research to determine the phytochemical content of *C. latifolia*, to analyze the organoleptic sweetness level of *C. latifolia* fruit and to analyze the anti-diabetic potential of *C. latifolia* plant extracts on diabetic mice. The study was conducted experimentally using 6 treatment levels and 4 replications. Prior to treatment, mice were induced hyperglycemia using alloxan 150 mg/kg WB were induced subcutaneously. The treatment being tested was oral Ethanol crude extract (ECE) for 28 days with 400 mg/kg WB, namely: G1: oral mineral water; G2: glibenclamide ; G3: ECE leaf; G4: ECE root; G5: ECE fruit and G6: ECE tree. Blood sugar levels were measured at 0, 7, 14, 21 and 28 days after oral ECE. Therefore, respondents stated that after consuming the fruit, they had a sweet-tasting and taste-modifying mineral water with a strength of 82.40 ± 8.36%, but the fruit extract did not show any sweet-tasting and taste-modifying. ANOVA results showed that oral ECE administration had a significant effect low on blood sugar levels. the HSD test was carried out with a 95% confidence level. ECE *C. latifolia* showed positive results on the tests of flavonoids, phenolics, saponins, alkaloids, triterpenoids and tannins. G4 was effective in reducing sugar levels after short time and G5 for 28 days (long time). C. *latifolia* have pharmacology effects to lower sugar levels and has taste modifying to sweetness.

Keywords: blood glucose; ethanol crude extract (ECE); hypoglycemic effect

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INTRODUCTION

The number of people with diabetes mellitus in Indonesia in 2019 was reported at 10.7 million. Indonesia ranks in the top seven in the world (Saeedi *et al*., 2019). Diabetes Mellitus is a non-communicable degenerative disease that occurs due to the failure of the pancreas to produce insufficient insulin or insensitivity to insulin. Insulin is a hormone synthesized by pancreatic beta cells that functions to lower the body's blood sugar levels to the optimal setting of blood glucose homeostasis. Patients with diabetes mellitus are characterized by high levels of sugar in the blood (hyperglycemia) and polyuria. In humans, hyperglycemia is characterized by glucose titers of ≥ 200 mg/dL (Al-Goblan *et al*., 2014).

In experimental animals of rodentia species, hyperglycemia can be obtained by inducing alloxan (Bukhari *et al*., 2015; Oshkondali *et al*., 2019). Alloxan is an organic component of urea derivatives which is a cytotoxic glucose analogue. The dose of alloxan to induce diabetes in test animals ranges from 90-200 mg/kg BW, while the optimal dose is 150 mg/kg BW (Oshkondali *et al*., 2019). The action mechanism of alloxan is to degrade pancreatic beta cells. Alloxan causes pancreatic beta cells to absorb the GLUT2 glucose transporter. The more sugar transporters in the cells, the more reactive oxygen stress (ROS) increases and pancreatic beta cells become lesions so that the body experiences insulin deficiency and increased hyperglycemia. Researchers have chosen alloxan because of its availability and it is cheaper than streptomyzin (Ighodaro *et al*., 2018).

Antidiabetic drugs used by patients with diabetes mellitus include metformin, glibenclamide, glimepirid, insulin aspart and insulin detemir (Khan *et al*., 2012). The use of

antidiabetic drugs can cause potential side effects based on the measurements of the Naranjo algorithm. Glibenclamide has the potential to cause hypoglycemia 15.79% (definite) side effects, metformin and glimepiride have the potential to cause nausea with definite values of 18.53% and 13.33% respectively (Putra *et al*., 2017). Metformin has been reported to cause lactic acidosis (60%) and vitamin B12 deficiency (30%) (Khan *et al*., 2012). So the use of natural medicines derived from plants is needed in the prevention and treatment of diabetes (Lü *et al*., 2009).

Plants of the genus *Curculigo* contain various secondary metabolites such as sweet-tasting and taste-modifying bioactives (Zhu *et al*., 2015), antidiabetic (Ge *et al*., 2014). Based on research, administration of *Curculigo orchioides* root extract was able to significantly reduce blood sugar levels in alloxan-induced albino rats (Madhavan *et al*., 2008). Administration of *Curculigo latifolia* root extract was also reported to have antihyperglycemic qualities (Zabidi *et al*., 2019). *Curculigo latifolia* in Indonesia is known as a plant with local names as *marasi* or *sukkit* (Silalahi *et al*., 2019) and *lemba* (Ranjbarfard *et al*., 2014). Based on the results of research originating from Malaysia, it was shown that the extract of the roots of *marasi* (*Curculigo latifolia*) contained phenolic derivatives (phloridzin, scandenin, pomiferin, monobenzone, mundulone, dimethyl caffeic acid, hydroquinone), hordatine A, ubiquinone, 3-methylsuberic acid, emmotin A rubratoxin B, and frangulin B (Zabidi *et al*., 2019). The aims of this study were to determine the phytochemical content of *C. latifolia*, to analyze the organoleptic sweetness level of *C. latifolia* fruit extract and to analyze the antidiabetic potential of *C. latifolia* plant extract on the blood profile of type II diabetic mice. This research provide information on the effectiveness of *C. latifolia* extract to lower blood sugar levels, it can be used as an antihyperglycemic therapeutic and the development of herbal medicines for diabetics so they can still taste sweet.

METHODS

This research was conducted at the animal house of Biology Laboratory, Faculty of Science and Technology, Muhammadiyah University Bandung. Before the research started, an Ethical Approval Letter was obtained for Health Research Using Animals as Research Subjects from the Research Ethics Committee of 'Aisyiyah University Bandung (Number: 244/KEP. 01/UNISA-BANDUNG/VIII/2022). This research starts from August-November 2022.

This study was conducted experimentally with a completely randomized design. The treatments tested were the types of extract *C. latifolia* and each sample was repeated 4 times.

Group	Information	References
G1	: control (oral water)	
G2	: glibbenclamid 1mg/kg BB	(Choy et al., 2021)
G3	: leaf extract 400mg/kg BB	(Oliyaei et al., 2021)
G4	: root extract 400mg/kg BB	(Oliyaei et al., 2021)
G5	: fruit extract 400mg/kg BB	(Oliyaei et al., 2021)
G6	: whole exctract tree 400mg/kg BB	(Oliyaei et al., 2021)

Extraction of *C. latifolia*

Sources of extracts come from samples of leaves, roots, fruits and whole plants. The samples were washed clean and then dried under the sun for 3 days, afterwards simplicia was made using a blender. Leaf simplicia extraction was carried out by mixing the simplicia in 96% ethanol solvent for food grade (1:10 w/v). This mixture is homogenized in a glass for 48 hours at room temperature, the solution is filtered using filter paper until a clear solution is obtained. This stage is called the maceration stage. The clear solution was evaporated using a rotary evaporator at 77°C until the remaining solvent was removed (Purba *et al*., 2020).

Phytochemical Test of *C. Latifolia* Extract

Flavonoid Test

C. latifolia extract was put into a test tube as much as 1 ml. Three drops of concentrated HCL and 0.002 gr of magnesium (Mg) powder was added to the *C. latifolia* extract. The test sample was left for 1 minute and the color change was observed.

Phenolic Test

C. latifolia extract was put into a test tube as much as 1 ml. Three drops of 1% FeCl3 solution was added to the *C. latifolia* extract. The test sample was left for 1 minute and the color change was observed.

Saponin Test

C.latifolia extract was put into a test tube as much as 2 ml. One drop with of concentrated HCl was added to the *C. latifolia* extract. The test sample was left for 1 minute and observed for changes in the formed foam.

Alkaloid Test

C. latifolia extract was put into a test tube as much as 1 ml. Three drops of Dragendroff reagent was added to the *C. latifolia* extract. The test sample was left for 1 minute and the color change was observed.

Triterpenoid/ Steroid Test

C. latifolia extract was put into a test tube as much as 1 ml. Three drops of Liebermann-Burchard reagent was added to the *C. latifolia* extract. The test sample was left for 1 minute and the color change was observed.

Tannin Test

C.latifolia extract was put into a test tube as much as 1 ml. 2-3 drops of 1% FeCl3 solution was added to the *C. latifolia* extract. The test sample was left for 1 minute and the color change was observed.

Preparation of Animal Cage

Cages with ventilated covers with husks on the bottom of the cage. The cages were 30x23x10 cm^3 in size, each cage was filled with four mice.

Preparation of Test Animals

Twenty-four male mice (*M. musculus*) BALB/c strain were sexually mature and weighed around 25.41-33.35(28.55±2.26g). Prior to the study treatment, mice were acclimatized for 7 days. The mice were confirmed to be healthy and normal (mice that were not disabled and were actively moving).

Provision of Treatment and Maintenance

Mice are divided into treatment levels, namely G1, G2, G3, G4, G5 and G6. Mice were given 4 g/mice of food every day. Provision of drinking water is given ad libitum. Lighting comes from light bulbs which are turned on at 08.30-14.00. Room temperature was 29℃. On day 0, mice were induced subcutaneously by alloxan (Eriani *et al*., 2021; Ratnaningtyas *et al*., 2018; Susanti *et al.*, 2019; Yuneldi *et al*., 2018) at a dose of 150 mg/kg BW (Nugraheni & Tjahjono, 2013). On day 7^{th}, the mice had a hyperglycemic effect which was marked by increased blood sugar levels between 200-600 mg/dl, husks wet because the urine titer increased and the mice were not active. Mice were given oral extract once a day for 28 days. The oral volume of the extract administered was 0.3mL.

Data Collection

At minutes 0, 60, 120 and 180 and days 7, 14, 21 and 28 after alloxan injection, blood sugar levels were measured. Blood sampling was carried out in the tail area. Blood sugar measurements were carried out using the sinocare safe AQ Smart tool and the sinocare safe AQ Smart strip. On day 28, mice were killed by cervical dislocation and dissected to remove the pancreas organ. The pancreas is weighed for the calculation of the pancreatic index.

Data Analysis

Sugar profile data were analyzed using one way ANOVA. The blood sugar profile data showed significant results, therefore the Tukey HSD test was further carried out. Data analysis was performed using SPSS version 16.

RESULTS AND DISCUSSION

Phytochemical content of *C. latifolia* extract

The results of the extraction of the leaf organs showed solid results and green extracts. Root and fruit extracts have a liquid character and are brown in color. Based on the phytochemical test, *C. latifolia* extract has different content in each organ. The root extract has positive results for the 6 tests performed. The phytochemical profile can be seen in Table 1. Morphology of *C. latifolia* can see in Figure 1.

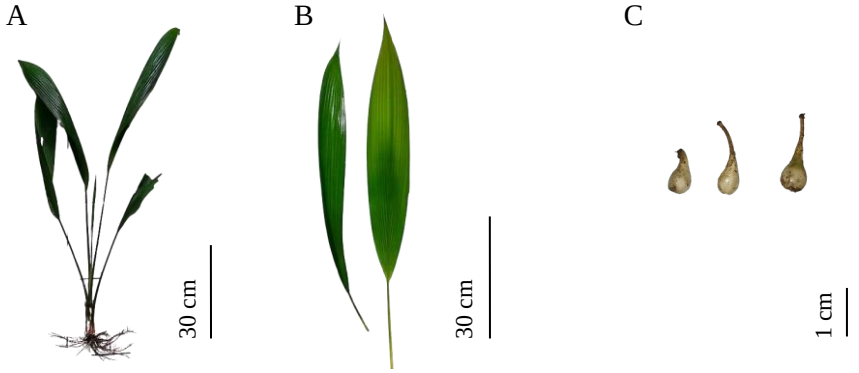

Figure 1. Morphology of *C. Latifolia* (A) Habitus, (B) Leaf, (C) Fruit

Table 1. Phytochemical content of *C. latifolia* extract

Extract	Flavonoid	Phenolic	Saponin	Alkaloid	Triterpenoid	Tannin
Leaf	+	+	-	+	+	+
root	+	+	+	+	+	+
Fruit	+	+	+	+	+	-
Whole tree	+	+	+	+	+	+

Organoleptic characteristics of sweetness level of *C. latifolia* fruit extract

Based on organoleptic tests on 10 woman respondents aged 19-26 years, it showed that the sweet taste of mineral water was 0%, while after consuming *C. latifolia* fruit, the respondents stated that there was a change towards a sweeter taste. The level of sweetness of mineral water after consuming *C. latifolia* fruit ranged from 70% - 99% (82.40 ± 8.36%). While the organoleptic test of *C. latifolia* fruit extract was 0 or the extraction was unable to maintain sweet-tasting and taste-modifying

Therefore, consuming *C. latifolia* increases the sweet taste of bland food or drinks, which is true according to previous research. This sweet taste arises from curculin type proteins. The results showed that *C. latifolia* extract had a sweetness 5 times that of sugar (Ishak *et al*., 2013). *C. latifolia* which is dried in the sun can damage curculin, so an appropriate technology is needed to preserve curculin in *C. latifolia* fruit. The fruit of *C. latifolia* spoils very quickly after ripening.

Profile of Blood Sugar Levels in Alloxan-Induced Mice in Minutes

Based on the research results, the blood sugar profile in the minutes after oral administration ranged from 132.00 to 147.00 mg/DL. Based on the results of the ANOVA analysis, the blood sugar profile at 0 and 60 minutes was not significant ($p>0.05$), while the blood sugar profile at 120 and 180 minutes after oral administration was significant ($p<0.05$). G4 was the most effective in reducing blood sugar levels. It can be said that the root extract of 400 mg/kg BW is effective in lowering blood sugar levels. The results of the study show similarities with research (Zabidi *et al*., 2019) that the highest anti-diabetic nutrigenomic content comes from the root of *C.latifolia* (Zabidi *et al*., 2019) (Table 2).

Table 2. The effect of various extract on Blood glucose concentration (mg/dL) on alloxan-induced diabetes in a male *Mus muscullus* in minutes

Group	0 minutes	60 minutes	120 minutes	180 minutes
G1	147.00±25.70^{a}	162.75±47.25^{a}	186.25±43.65^{b}	133.25±9.50^{bc}
G2	133.00±4.24^{a}	113.75±22.90^{a}	134.75±44.54^{ab}	93.75±9.84^{ab}
G3	132.00±19.87^{a}	138.25±18.08^{a}	125.75±36.22^{ab}	103.25±16.70^{ab}
G4	145.50±17.41^{a}	119.25±20.37^{a}	113.50±14.20^{a}	85.50±7.05^{a}
G5	138.75±20.93^{a}	140.75±40.94^{a}	128.75±8.26^{ab}	115.25±15.28^{bc}
G6	130.00±10.23^{a}	146.00±36.62^{a}	112.50±12.92^{a}	105.00±13.83^{ab}

Annotation description: different superscrift letter showed significant results with the tukey HSD test at the 95% confidence level.

Profile of Alloxan-Induced Blood Sugar Levels in Mice in 28Days

Based on measurements of blood sugar levels on day 7 after oral administration, it showed 174.75-557.75 mg/DL. Blood sugar levels on day 14 after oral administration ranged from 138.50 to 514.00 mg/DL. Blood sugar levels on day 21 after oral administration showed 155.00-532.25 mg/DL. Blood sugar level on day 28 after oral administration showed 142.00-409.75 mg/DL.

Based on the results of the ANOVA analysis, the blood sugar profile at 7,14,21 and 28 days of treatment was significant ($p<0.05$). In this study, the dose of glibenclamide 1 mg/kg BW had relatively the same effect as the doses of G3, G4, and G6. On the 28th day, blood sugar levels at G5 showed 199.00 ± 74.89 mg/dL. However, in this study the blood sugar levels of mice were still categorized as type 2 diabetes mellitus because their blood sugar levels were more than 200 mg/DL (Table 3).

Table 3. The effect of various extract on Blood glucose concentration (mg/dL) on alloxan-induced diabetes in a male *Mus muscullus* in days

Group	0 days	7 days	14 days	21 days	28 days
G1	147.00±25.70^{a}	174.75 ±51.88^{a}	138.5 ±31.75^{a}	155.00 ±55.59^{a}	142.00±32.69^{a}
G2	133.00±4.240^{a}	557.75 ±84.50^{c}	514.00±122.10^{c}	448.00 ±126.76^{ab}	358.25±83.01^{ab}
G3	132.00±19.87^{a}	503.00±129.65^{bc}	474.50±146.97^{ab}	476.25 ±247.50^{ab}	409.75±178.94^{b}
G4	145.50±17.41^{a}	496.00±120.31^{bc}	381.50±229.05^{ab}	532.25 ±86.60^{c}	391.00±74.13^{b}
G5	138.75±20.93^{a}	276.25±131.68^{ab}	370.25±135.50^{ab}	486.25 ±234.83^{ab}	199.00±74.89^{ab}
G6	130.00±10.23^{a}	459.75 ±162.99 ^{bc}	426.25±200.66^{ab}	405.50±146.87^{ab}	361.50±98.78^{ab}

Annotation description: different superscrift letter shows significant results with the Tukey HSD test at the 95% confidence level.

Glibenclamide is an oral drug for diabetics. Glibenclamide has a mechanism to stimulate insulin secretion (Riefflin *et al*., 2015). In several previous studies, the effective dose of glibenclamide in mice strain balb/c was 3 mg/20 g BB which provided antidiabetic effect after 7 days of treatment (Salehi *et al*., 2019). Whereas in swiss webster strains mice, the effective dose of glibenclamide is 0.65 mg/kg BB which provides an antidiabetic effect after 30 minutes of treatment (Ifada *et al*., 2021). The reduction in blood sugar levels in this study was possible due to *C.latifolia* bioactive compounds such as alkaloids, phenols, tannins, saponins, terpenoids.

The content of flavonoids is reported to regenerate the islets of Langerhans cells in the pancreas organ. Alkaloid compounds and polyphenols regenerate pancreatic β cells and increase glycogenesis. Alkaloid compounds work by becoming inhibitors of the alpha-glucosidase enzyme found in the duodenum mucosa which causes the decomposition of polysaccharides into monosaccharides to be inhibited, so that the glucose released will be inhibited and absorption into the blood will be slow (Yu & Xu, 2020). Saponins can stimulate the release of pancreatic insulin (a hormone that stimulates a decrease in blood sugar levels in homeostasis) (Barky *et al*., 2017). Saponins can increase the permeability of the intestinal membrane causing glucose absorption to be inhibited. In addition, saponins can increase the number of beta cells in the pancreas by regenerating cells in the pancreas so that insulin levels will increase (Alam *et al*., 2022).

Polyphenol compounds lower blood sugar by becoming inhibitors of the enzymes alpha-glucosidase and alpha-amylase, increasing insulin secretion, and resisting the release of glucose in the liver (Zhao *et al*., 2020). Triterpenoid compounds working as antioxidants can inhibit the trigger for the emergence of ROS in DM sufferers by repairing beta cells on the Langerhans islands so as to protect pancreatic cells from free radicals, as a result of which insulin can continue to be produced so that blood sugar levels can be reduced (Barreiro *et al*., 2022). Flavonoid compounds are secondary metabolites that act as antidiabetics by becoming inhibitors of the enzyme alpha glucosidase so that there is no breakdown of carbohydrates into glucose. In addition, flavonoids can also increase blood sugar accumulation by increasing glycogenesis. (Al-Ishaq *et al*., 2019). Tannin compounds have the potential to be antidiabetic because they can lower blood sugar by increasing sugar transport through signaling akivation mediated by insulin (Al-Ishaq *et al*., 2019). *C.latifolia* root extract has antidiabetic and hypoglymic abilities because it increases the expression of IRS-1, GLUT4, PPARά, PPARβ, IGF-1, AdipoR1, AdipoR2, leptin, LPL, lipase genes in adipose tissue and muscle tissue in diabetic rats. *C.latifolia* regulates genes in the process of sugar and fat metabolism (Ishak *et al*., 2013).

The results showed that the weight of the pancreas in mice that were not induced by alloxan ranged from 0.18-0.22g. Alloxan-induced mice ranged from 0.16-0.30g. The ratio of the weight of the pancreas to body weight is known as the pakreas index. The results of ANOVA showed that the oral administration of *C. latifolia* ECE was significant for the hyperglycemic mice pancreas index $p<0.05$. Based on the Tukey HSD test, the pakreas index on G1 was the lowest, while the highest pakreas index was on G2 (Table 4).

Table 4. The effect of various extract on pancreas index (%) on alloxan-induced diabetes in a male *Mus muscullus*

Group	Pancreas index (%)
G1	0.56±0.09^{a}
G2	1.01±0.36^{b}
G3	0.65±0.14^{ab}
G4	0.76±0.08^{ab}
G5	0.82±0.10^{ab}
G6	0.73±0.17^{ab}

Animals tested for hyperglycemia due to injection of alloxan 120 mg/kg BW, namely more than 3/4 of the structure of the cells that make up the pancreas experienced necrosis (Susanti *et al*., 2019). The islets of Langerhans are narrower, the β-cell population shrinks, the cell nucleus shrinks, and the cytoplasm fades in the structure of the pancreas of hyperglycemic test animals compared to healthy test animals (Osibemhe *et al*., 2023). In this study, the high pancreatic index in aloxan-induced mice was thought to be because the mice had fatty in the pancreas and pancreatic beta cells experienced hyperthropy and hyperpacia. According to (Bhanudas & Gopal, 2016) after 28 days of rats induced alloxan 120mg/kg BW the structure of the pancreas was hypertrophied (Susanti *et al*., 2019). Fat infiltration of the pancreas causes hypertropy and hyperplacua of pancreatic cells. Fatty can cause a decrease in the function and population of pancreatic beta cells in diabetics. Higher levels of pancreatic fat had a correlation with pre-diabetes (Silva *et al*., 2021).

The novelty in this study is in the form of the use of extracts of leaves, fruits, and whole plants. Previous research only used extracts derived from the root (Zabidi *et al*., 2019). In the study, fruit extract 400mg/kg BW gave an optimal effect compared to other extracts. This information provides benefits for diabetics to consume this *C. latifolia* fruit. In this study, the fruit used was still in the stage of not fully ripe so that organoleptic results showed sweetness in the fruit after consuming fresh fruit but the results of fruit extract did not produce sweetness. Further research is expected to use *C. latifolia* fruit that has been fully ripe, and research is needed on the profile of the fruit maturity cycle and getting ripe fruit.

CONCLUSION

Based on the results and discussion, it can be concluded respondents stated that after consuming the fruit, they had a sweet-tasting and taste-modifying mineral water with a strength of 82.40 ± 8.36%, but the fruit extract did not show any sweet-tasting and taste-modifying. The ECE has antidiabetic therapeutic potential with G4 effectively reducing sugar levels after 180 minutes of treatment, while oral G5 for 28 days effectively reduced alloxan-induced male mice blood sugar levels. It is necessary to conduct research related to the structure of the pancreas of diabetic mice after administration of *C. latifolia* extract.

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