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Antidiabetic effect and glucose tolerance of areca nut (*Areca catechu*) seed ethanol extract on alloxan-induced diabetic male rats

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Antidiabetic effect and glucose tolerance of areca nut (*Areca catechu*) seed ethanol extract on alloxan-induced diabetic male rats

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Abstract. Areca catechu fruit (Areca nut) is one component of betel chewing. There is an assumption that the antidiabetic effect of chewing betel is sourced from areca nut. This study aims to determine the anti-hyperglycemic effect and glucose tolerance of ethanol extract of areca nut (*Areca catechu*) seed in diabetic rats. Old Areca nut fruit was obtained from a garden in the Depok region, the suburb of Jakarta. Areca nut seeds were made into a fine powder, then macerated by using 70% ethanol at room temperature based on the Harbone method. Male rats were eligible for the trial; after acclimatization, rats were made diabetic by using alloxan. The rats for this trial were divided into 6 groups. Each of groups consisted of 5 rats. Glibenclamide was used as a positive control for anti-diabetic, and acarbose was used for glucose tolerance test, as normal control was given distilled water, while negative control was used 1% CMC Na, namely a solution suspending agent for test preparation. Areca nut seed extract was given with 3 types of doses, namely low, medium and high doses, namely 22.5 mg; 45 mg and 180 mg per 200 gr body weight (BW) rats, respectively. For measure blood, sugar levels were used as a glucometer tool. The result of this study showed that on 14 days of given test preparation, the statistical results with ANOVA test and Kruskal-Wallis test showed that medium doses of areca nut seed extract had the same anti-diabetic effect and glucose tolerance with positive control and were significantly different to negative controls. ($P \leq 0.05$). While on the low and high dose was not significantly different from negative controls ($P \geq 0.05$). Conclusion of this study, areca nut seed was very potential for antidiabetic and glucose tolerance.

1. Introduction

Diabetes is a complex chronic disease that requires continuous medical care with multifactorial risk reduction strategies because diabetes can weaken almost all organs of the body. The most important thing in controlling diabetes risk is controlling blood sugar levels not to become hyperglycemic and also hypoglycemic, namely; before meals, around 70-130 mg/dL, 2 hours after meals, less than 140 mg/dL, after not eating (fasting) at least 8 hours, less than 100 mg/dL and at the time of going to sleep: 100-140 mg/dL [1,2].



At this time, there are no diabetes drugs that are truly ideal to be able to maintain the same blood sugar as the condition of normal people's blood sugar, as mentioned above, while the number of people living with diabetes in the world is increasing from time to time [2,3].

The International Diabetes Federation (IDF) estimates that 1 in 11 adults aged 20 -79 years, or there were about 415 million adults who had diabetes mellitus globally in 2015. According to the World Health Organization (WHO), In 2017, there were about 150 million people have diabetes mellitus worldwide. This estimate is projected to rise to 642 million in 2040 [3,4]. At this time, generally, diabetes medications used have many side effects, and the price is quite expensive. Therefore, at this time, it is very necessary to look for new drugs that are safer, cheaper and have better efficacy for patients who have diabetes mellitus [4].

Based on the results of research from Mondal et al. (2012), Areca catechu leaves are known to be efficacious as anti-diabetic, while for areca nut, there are two different opinions. The first opinion is that said, betel nut consumed by chewer betel addicts with a frequency more than 12 times per day is a trigger for cancer, especially the oropharyngeal cancers. *In vivo* studies in animal models have reported that prolonged areca nut chewing leads to increase in serum aminotransferases level that results in abnormal liver function, therefore, chewing betel addiction should be banned by medical personnel and the government because the content of alkaloids in the areca nut is a trigger for cancer [5,6,7,8,9]. Consuming excessive amounts of areca nut by betel chewer will also trigger hyperglycemic occurrence [10].

The second opinion is the researchers who say that chewing betel is very good for health as long as it is not over-consumed. According to Bhat et al. (2017 & 2018) the opinion that Chewing betel is harmful to health is a result of research that is not objective, because the things highlighted are those people who are addicted to chewing betel by consuming too much, even though all medicinal plants that are consumed in excess are harmful to health. The history of chewing areca nut is not just known, but it has been known since around 1300BC and chewing betel nut has long been felt and believed by betel chewers has many benefits for health and is used by around 700 million people, especially in the South Asian region, Southeast Asia, China, Taiwan and several other countries in the Asia Pacific region. Areca nut is traditionally used to treat several ailments as it has properties such as antibacterial, anti-heartburn, antiulcer, antidiarrheal, anthelmintic, antimalarial, antihypertension, carminative, digestive, diuretic, laxative, pro healing, etc. [5,11,12]. Therefore, our research can answer the differences of opinion between the two groups about the efficacy of areca nut as antidiabetic, as well as to get new drugs for diabetics.

2. Materials and methods

Old Areca nut fruit was obtained from a garden in the Depok region, the suburb of Jakarta, and sample taxonomy determination was carried out at the Biology Research Center, Indonesian Institute of Sciences, Cibinong, Bogor, Indonesia.

The areca nut seed preparation was made by maceration using 70% ethanol based on Harbone's method. The maceration process was carried out as follows; The old Areca nut was taken their seeds and mashed with a blender, 300 g of areca nut seed powder was extracted by repeated maceration method by using 70% ethanol and occasionally stirred until the solution obtained was clear. The filtrate obtained was evaporated by using a vacuum evaporator. The yield calculation was done by calculating the amount of dry extract obtained against the amount of powder before extraction, then multiplying by 100% [13].

Screening groups of chemical compounds on areca nut seed extract was carried out based on Harbone's method, the presence of chemical compound groups was carried out for groups of alkaloids, flavonoids, saponins, steroids, triterpenoids, tannins, quinones, and essential oils [13].

The male white rats, a strain of Sprague-Dawley with 3.5-4 months old (weight 170-230 g) were obtained from the Faculty of Veterinary Medicine, Bogor Agricultural Institute, Indonesia. This study was carried out in the animal house of Faculty of Medicine and Health Sciences, State Islamic University, Syarif Hidayatullah Jakarta before the experiment was carried out, the rats were acclimatized for 7 days and maintained on 12 hours light, 12 hours dark cycle on temperature 24 – 27

°C. The rats were given standard pellet diet and water *ad libitum* and kept under standard conditions in animal houses based on norms of the Committee for Control and Supervision on Experiments on Animals (CPCSEA) [14].



Figure 1. Areca tree, areca nut, and areca nut seed

The number of rats per group for experiments was calculated based on the Federer formula: $(n-1) \cdot (t-1) = (6-1) \cdot (4-1) > 15$, or the number of rats for each group must be greater than 4 rats. In this study, the animals were divided into 6 groups. Each group consists of 5 rats [15].

The experimental rats were made to have diabetes by administering alloxan through intravenous injection. Measurement of rat blood was carried out before giving alloxan, and alloxan doses were calculated based on effective doses to make rats become diabetic, i.e., 13 mg / 200 g BW rats. Usually, on days 7 to 14, the blood sugar levels of rats stabilize with diabetes [16].

In this study, before giving the test preparation, the animals have fasted for 14 hours. Acarbose was used as a positive control for glucose tolerance testing, and glibenclamide used as a positive control for anti-hyperglycemic. The dose of acarbose and glibenclamide given to rats was calculated based on the conversion of Paget and Barnes, i.e., the dose for every 200 g of rats is equivalent to 0.018 x human dose, in this case, the effective dose for humans is 50-200 mg/kg for acarbose and 5-10 mg/kg BW for glibenclamide [16].

The administration of test preparation to experimental animals for glucose tolerance test as shown in table 1. In this study, glucose was given 50% glucose with a dose 1 g/kg BW. Observation for glucose tolerance test on animal experiments was carried out at 0; 30; 60; 90 and 120 minutes after administration of the test preparation by taking rat blood through intravenous rat tail, and their blood sugar levels were measured using a glucometer [16].

Table 1. Treatment of 6 groups of rats for glucose tolerance test

No	Rats	Treatment
1	5	Diabetic rats were given areca nut seed extract 22.5 mg in 1% CMC Na, 50% glucose in aquadest, each 1 ml/200 g BW (Low dose)
2	5	Diabetic rats was given areca nut seed extract 45 mg in 1% CMC Na, 50% glucose in aquadest, each 1 ml/200 g BW (Medium dose)
3	5	Diabetic rats was given areca nut seed extract 180 mg in 1% CMC Na, 50% glucose in aquadest, each 1 ml/200 g BW (High dose)
4	5	Diabetic rats was given acarbose 1,8 mg in 1% CMC Na, 50% glucose in distilled water, each 1 ml/200 g BW (Positive control)
5	5	Rats were just given aquadest 2 ml/200 g BW (Normal control)
6	5	Diabetic rats was given 50 % glucose in aquadest, 1%, CMC Na, each 1ml/200 g BW (Negative control)

Meanwhile, for the anti-hyperglycemic test, administration of test preparations for experimental animals was conducted every day and the process of administration of test preparation, as shown in table 2. Observations for the anti-hyperglycemic test in experimental animals were carried out on day

0; 14; 17; 22; and 28, by taking rat blood through intravenous rat tail, and their blood sugar levels were measured using a glucometer [16].

According to research from Sari et al., the areca nut LD50 is greater than 15000 mg/kg BW, therefore dosing for areca nut seed can be below 15000 mg/kg BW [17].

In this study, the doses used were 22.5 mg / 200 gr BW for low dose, 45 mg/200 gr BW for medium dose, and 180 mg / 200 gr BW high dose. The administration of the test dosage for the 6 experimental animal groups was as shown in table 1.

Table 2. The administration of test preparation per day to the experimental animal for anti-hyperglycemic test

No	Rats	Treatment
1	5	Diabetic rats was given areca nut seed extract 22,5 mg in 1% CMC Na with dose 1ml/200 g BW (Low dose)
2	5	Diabetic rats was given areca nut seed extract 45 mg in 1% CMC Na with dose 1ml/200 g BW (Medium dose)
3	5	Diabetic rats was given areca nut seed extract 180 mg in 1% CMC Na, aquadest, with dose 1ml/200 g BW (High dose)
4	5	Diabetic rats was given glibenclamide 0,09 mg in 1%, CMC Na, with dose 1ml/200 g BW (Positive control)
5	5	Rats were just given aquadest 1ml/200 g BW (Normal control)
6	5	Diabetic rats were given 1%, CMC Na with dose 1ml/200 g BW (Negative control)

3. Results and discussions

The results of plant authentication were carried out by the Indonesian Institute of Sciences Biology Research Center, Bogor, Indonesia. stated that, the plants used for this study were areca nut (*Areca catechu*)

The results of maceration of 300 g areca nut seed powder carried out with 70% ethanol, and dried by using a vacuum rotary evaporator was obtained yield about 75 g (25%).

The results of the chemical group examination of the areca nut seed extract compound, as shown in Table 3.

Table 3. The content of groups of chemical compounds of Areca nut seed extract

Chemical groups	Results
Alkaloids	+
Flavonoids	+
Tannin	+
Quinone	+
Steroids & Triterpenoids	+
Saponin	+
Essential oil	-
Coumarin	-

Comparison of the results of the average measurement of blood sugar levels for glucose tolerance test from the test preparation at minute 0; 30; 60; 90; 120; 150 and 180, as shown in table 4.

Diagram of comparison of the results of the average measurement of blood sugar levels for glucose tolerance test from the test preparation at minute 0; 30; 60; 90; 120; 150 and 180,

The chart of comparison of the results of the average measurement of blood sugar levels for glucose tolerance test from the areca nut seed extract, positive control, negative control and normal control at minute 0; 30; 60; 90; 120; 150 and 180, as shown in figure 2.

Table 4. The average results of the measurement of blood sugar levels for glucose tolerance test of test preparation

Minutes	Low Dose	Medium Dose	High Dose	Normal Control	Negative Control	Positive Control
0	118.53 ± 35.37	119.51 ± 31.00	117.23 ± 1.35	86.76 ± 19.70	122.75 ± 20.35	108.26 ± 3.51
30	148.51 ± 30.05	122.53 ± 14.20	132.01 ± 25.44	106.75 ± 20.61	161.74 ± 20.35	114.24 ± 18.63
60	126.49 ± 27.33	136.03 ± 20.80	122.24 ± 19.57	123.01 ± 42.58	280.76 ± 30.10	103.73 ± 14.10
90	128.52 ± 9.26	155.48 ± 39.77	142.23 ± 31.15	133.51 ± 56.55	285.24 ± 11.79	118.53 ± 11.62
120	139.53 ± 31.89	133.25 ± 17.13	158.03 ± 30.28	134.25 ± 78.72	244.51 ± 19.14	106.51 ± 23.39
150	140.02 ± 38.70	148.01 ± 16.45	148.23 ± 25.75	111.02 ± 35.45	237.03 ± 19.14	110.53 ± 10.08
180	145.74 ± 43.96	163.25 ± 22.04	136.49 ± 25.94	105.03 ± 50.68	228.03 ± 10.71	132.23 ± 10.31

It has been recognized that alloxan at a dose of 13 mg / 200 g BW of rats will damage part of the pancreatic islets of the regions of the pancreas. This causes the amount of insulin secreted by pancreatic islets will decrease [18, 19].

Acarbose is an alpha-glucosidase inhibitor that works to inhibit the alpha-glucosidase enzyme found in the walls of the small intestine. Acarbose works by slowing the action of certain chemicals that break down food to release glucose into the blood. Slowing food digestion helps keep blood glucose from rising very high after meals. Glibenclamide is in the sulfonylureas class of medications and works by increasing the release of insulin from the pancreas [18, 19].

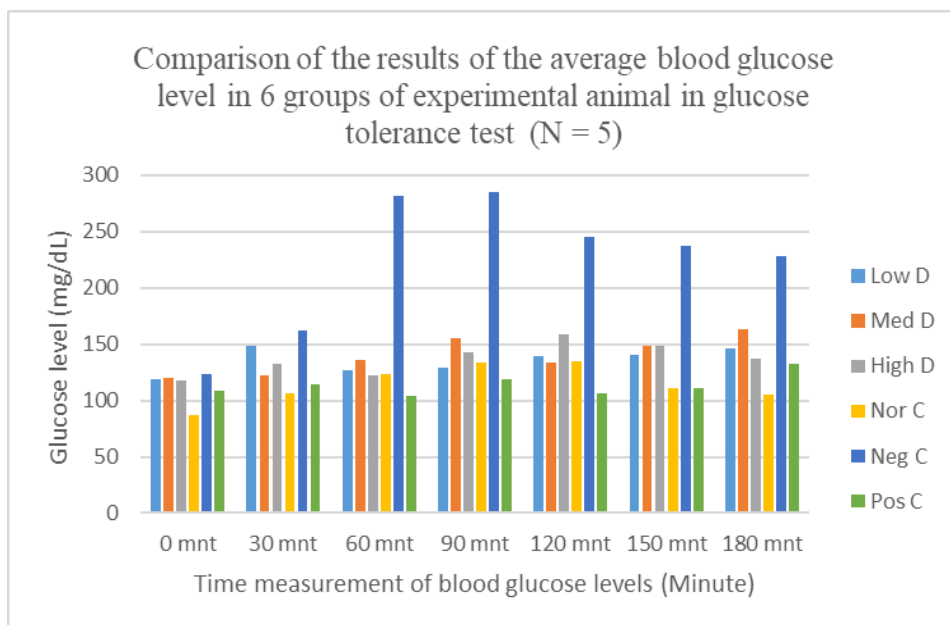


Figure 2. The chart of comparison of the results of the average measurement of blood sugar levels for glucose tolerance test

Note:
 Nor C = Normal control Pos C = Positive control Neg C = Negative control
 Low D = Low dose Mid D = Middle dose High D = High dose

As shown in table 4 and figure 2 Glucose tolerance test in negative control of rats that had diabetes, it was very apparent that the increase in blood glucose levels at 60 and 90 minutes and decreased slowly at 120, 150 and 180 minutes compared to at 0 and 30 minutes after the rat was fasted for about 14 hours. The results of the statistical test of the increase in blood glucose levels were significantly different ($P \leq 0.05$) at the time of measurement 60 minutes to 180 minutes compared to the measurement of time 0 minute.

Glucose tolerance test in rats that did not have diabetes or normal rats that were fasted for around 14 hours, glucose measurement results increase at a measurement time of 30 minutes and experience the highest increase at the time of measurement 60 minutes and decrease slowly from time to time at the time of measurement 90; 120; 150 and 180 minutes compared to the measurement time of 0 minute. The results of the statistical tests at the time of measurement 60 minutes to 120 minutes were significantly different ($P \leq 0.05$) compared to the measurement time of 0 minutes ($P \leq 0.05$).

The measurement results of glucose levels in the glucose tolerance test for areca nut seed extract for a low dose, middle dose, high dose, and positive control were significantly different compared to negative controls at a measurement time of 60 until 180 minutes ($P \leq 0.05$). While the results of statistical tests for low dose, middle dose, high dose. Only the high dose measured at 180 minutes was not significantly different compared to a positive control ($P \geq 0.05$).

As shown in table 5 and figure 3, in testing the anti-hyperglycemic effect, on day 0 before administration of alloxan, blood glucose levels were almost the same in all (6 groups) after rats were fasted for about 14 hours and the statistical tests did not show significantly different ($P \geq 0.05$). On the 14th day after administration of alloxan, there were increase in glucose levels in all groups of rats, except in the normal group not given alloxan. The results of the statistical test on the measurement of blood glucose levels on day 14 showed significantly different ($P \leq 0.05$) of the five groups given alloxan compared to the group of normal rats not given alloxan.

Table 5. The average results of the measurement of blood sugar levels for anti-hyperglycemic of test preparation

Days	Low Dose	Medium Dose	High Dose	Normal Control	Negative Control	Positive Control
0	89.23 ± 0,96	87.21 ± 3,20	86.77 ± 2,75	84.74 ± 3,59	83.74 ± 1,26	85.53 ± 3,41
14	135.25 ± 19,14	134.48 ± 19,28	139.49 ± 20,29	85.63 ± 2,08	110.75 ± 1,89	118.47 ± 10,47
17	132.03 ± 63,63	127.73 ± 13,72	137.02 ± 32,28	121.61 ± 2,08	130.24 ± 8,54	72.52 ± 27,38
22	101.52 ± 8,81	105.71 ± 8,81	107.53 ± 39,19	104.24 ± 12,97	158.26 ± 15,59	77.11 ± 24,45
28	99.99 ± 7,12	118.74 ± 23,96	91.2 7± 14,03	90.52 ± 22,69	152.11 ± 4,97	78.42 ± 12,66

In the negative group of rats, namely; the rats were made to have diabetes but not given the drug and not given the areca nut seed extract, in this case, there were increase in blood glucose levels from day 14 to day 28, statistical test results showed significantly different ($P \leq 0.05$) for blood glucose levels from day 14th until day 28th compared to day 0 before administration of alloxan.

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Measurement of glucose levels on the day 17th for administration areca nut seed extract in all groups showed no significantly different to negative control ($P \geq 0.05$), in this case, this means that areca seed extract did not yet affect an anti-hyperglycemic. While the measurement of blood glucose levels on day 22nd and day 28th of all the groups given the areca nut seed extract was compared to negative control, the results of the statistical test showed significantly different ($P \leq 0.05$) compared to

negative control. In this case, this means that the administration of the areca nut seed extract had worked as an anti-hyperglycemic.

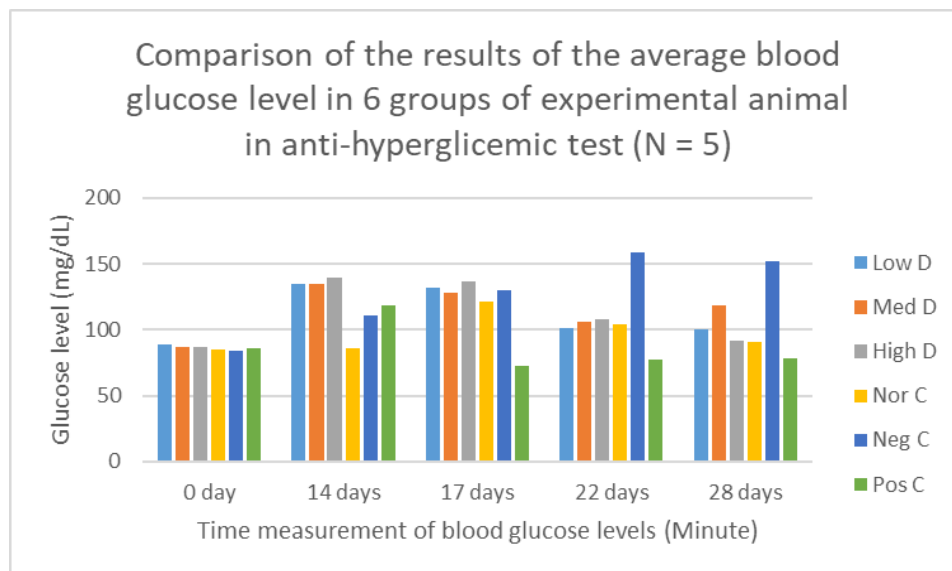


Figure 3. Comparison of the results of the average blood glucose level in 6 groups of rats in anti-hyperglycemic of test preparation

In the field of Pharmacology, compounds which have the same basic chemical structure and are different in functional groups, these compounds will have the same efficacy but differ in the level of efficacy [21, 22, 23, 24].

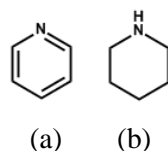


Figure 4. Structure of Alkaloid of Pyridine (a) and piperidine (b)

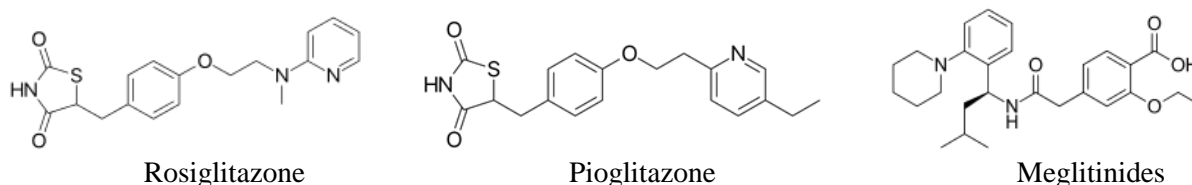


Figure 5. Alkaloid of Pyridine and piperidine groups that already used as drugs for diabetes Mellitus type 2.

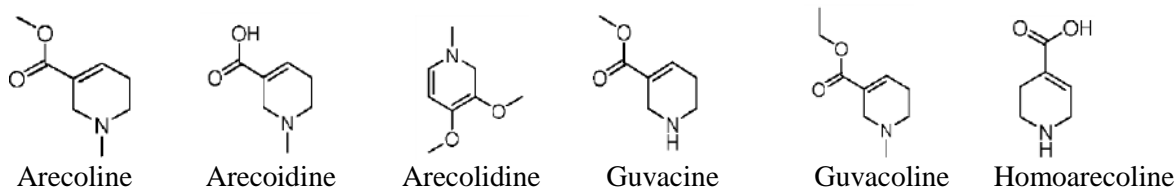


Figure 6. Alkaloid from areca nut which includes group alkaloid of pyridine and piperidine that suspected efficacious as antidiabetic

Plant alkaloids from the Pyridine and piperidine groups (figure 4) that have been known which have anti-diabetic properties, namely: Rosiglitazone with Avanda trade names, Pioglitazone with Actos trade names, Meglitinides with generic names Glufast, as shown in figure 5.

According to the results of research from Wei Peng et al. (2015) and Srimani et al. (2016), that areca nut contains Pyridine and piperidine alkaloids, which are Arecoline, Arecolidine, Arecolidine, Guvacine, Guvacoline, Homoarecoline, and Isoguvacine, as their chemical formula is shown in the picture Arecoline, Arecolidine, Arecolidine, Guvacine, Guvacoline, Homoarecoline and Isoguvacine [25, 26]. Therefore, strongly suspected, the efficacy of betel nut as an anti-diabetic comes from the Pyridine and piperidine alkaloids contained in betel nuts.

4. Conclusion

Areca nut (*Areca catechu*) seed ethanol extract was very potential for reduce blood glucose levels and glucose tolerance on Alloxan Induced Diabetic Male Rats, where the effect of reducing blood glucose levels is the best at a dose of 180 mg/200 g BW, while the effect for glucose tolerance is the best at a dose of 45 mg/200 gr BW

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