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Artocarpus altilis Extract Capsules Reduce Fasting Blood Glucose in Prediabetes

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Abstract

BACKGROUND: Management of prediabetes patients is essential to reduce the increased prevalence of type 2 diabetes. Prediabetes prevention strategies have been widely carried out with traditional medicine by the community.

AIM: This study aims to assess the effect of Artocarpus altilis extract on reducing fasting blood glucose of the patients in Maros Regency, Indonesia.

METHOD: The study was a double-blind, randomized controlled trial, dividing participants into intervention groups who received *A. altilis* extract (n = 37) and the control group who received placebo (n = 37). The assessment of fasting blood glucose through screening with a simple enzymatic method. A fasting blood glucose was then validated using the spectrophotometric method. The fasting blood glucose measurement was performed again after 28 days of intervention, besides physical activity, food intake, and education of prediabetes/diabetes prevention measurements. The *A. altilis* extract was developed after the cold maceration process using a freeze dryer at −60°C. The data were analyzed using chi-square, independent t-test, t-test, and Wilcoxon test.

RESULTS: Most participants were female (68.0%), 40–49 years (51.9%), and stay-at-home parent (70.3%). The baseline data reports all variables were not significantly different between the two groups (p > 0.005). There was a significant decline in the intervention group after the intervention (114.89 ± 6.6 vs. 98.73 ± 4.8, p < 0.001) and no changes in the control group (113.62 ± 6.6 vs. 113.59 ± 6.7, p = 0.768).

CONCLUSION: There is a significant reduction in fasting blood glucose in the intervention group who received *A. altilis* extract.

Introduction

People's lifestyles have changed as the economy and technology have progressed, such as the habit of consuming high-carbohydrate and fat foods, excessive junk food, alcoholic beverages, doing less physical activity, and smoking [1], [2]. Prediabetes is a global health problem that everyone should be concerned about because it is more common than type 2 diabetes mellitus (DM). Between 1999 and 2010, 35.5% of Americans aged 20 and up had prediabetes, compared to 35.5% in the UK, 15.5% in China, 14.8% in Spain, and 22.4% in Bangladesh [3]. while the prevalence of prediabetes in Indonesia reached 10.2% in 2009 and 36.6% in 2013 [4].

The condition of prediabetes is a determining factor in whether the patient will experience diabetes. It depends on whether prediabetes is detected earlier or experiences complications. Doing fasting blood glucose screening is very important to detect prediabetes. If this is found, therapy is faster so that the disease does not develop into type 2 DM. DM is a metabolic disease known as the silent killer because patients rarely realize that they have diabetes. When the initial health examination is carried out, many health complications are identified. This disease is also known as the mother of disease. People with DM are followed by other diseases, such as hyperlipidemia, hypertension, and complications such as heart and blood vessel disease, stroke, kidney failure, or blindness [5].

Indonesia has very diverse and abundant natural with huge potential herbal medicine could be used. Recently, studies in developing and using traditional medicines have been conducted to overcome health problems in the population. Herbal medicines such as plant extract might be cheaper and easier to obtain and have minor side effects [6]. The advantage of treatment by using traditional herbs is that it rarely causes severe side effects compared to synthetic treatment [7].

Many preclinical trial studies were conducted by using herbs to lower blood glucose levels. A study by Jafar *et al*. used cinnamon bark to explore the effect on prediabetes blood glucose levels. The study conducted in Makassar used a quasi-experimental randomized pre-test design using 10 g of cinnamon bark for 14 days. Each group was given education where 13 respondents were as the intervention group and 12 as the control group. The result of this cinnamon bark research can reduce prediabetes blood glucose levels by 4.14 mg/dL [8]. The research conducted by Mujianti (2018), used *Moringa oleifera* leaves, a quasi-experimental one-group pre and post-test, research location in the Sangurara Public Health Center Palu City 2018. There were 12 respondents. Giving Moringa leaves tea was as much as 250 ml (1 cup) 28 days, as much as three cups/day. The results of the study the Moringa leaves consumed 3 glasses/day reduces Fasting Blood Glucose levels by 13.42 mg/dL in type 2 DM [9].

Artocarpus altilis is a traditional medicine that Indonesian ancestors and other nations have long used. The chemical composition includes flavonoids, quercetin, saponins, polyphenols, tannins, hydrocyanic acid, antioxidant compounds can inactivate the development of oxidation reactions that can reduce or neutralize free radicals [10], [11]. Many preclinical studies of *A. altilis* such as Fitriani *et al*. (2019), used extracts (70% ethanol) of *A. altilis* at doses of 100 and 400 mg/kg of bodyweight. The conclusion is that *A. altilis* extract can reduce blood glucose levels in alloxan-induced DM rats for 14 days. Yulia *et al*.'s study (2019) used *A. altilis* extract 400 mg/kg of body weight (BW) that could significantly reduce blood glucose levels, which had the same effect as administering insulin (4 UI/200 mg). The purpose of this study was to examine the effect of *A. altilis* extract on fasting blood glucose of prediabetes patients.

Methods

Study design

This study was conducted in Maros Regency, Indonesia, from July 2020 to December 2020. This study was a double-blind, randomized controlled trial, pre, and post-test research design. The randomization was performed out using a simple random sampling technique. Respondents then chose the papers coded 1 and 2 by the researcher for the group assignment. The codes A and B were only known by the supervisors and the supplier of the capsules (*A. altilis* extract and placebo). Capsule A was given to group 1 and capsule B to group 2. Each group received an intervention for 28 days, with a fasting blood glucose examination every 7 days using the easy touch screening tool.

Study participants

There were 37 respondents from each group enrolled in this study. The inclusion criteria were having a fasting glucose level of 100–125 mg/dL, age 20–60 years, willing to consume *A. altilis* extract every day for 28 days, and having husband/wife/family. The exclusion criteria for this study were having a history of illness that required treatment, a history of previous DM, or being on DM treatment. To search for the prediabetes population, the researcher used the POSBINDU diabetes database (integrated coaching post) in collaboration with health workers and local cadres of the selected Puskesmas (Community health center in a sub-district) to screen for fasting blood glucose fasting 8–12 h for prospective respondents.

From the examination, the research team obtained 110 prospective respondents with a fasting blood glucose level of 100–125 mg/dL. Next, the research team will take ±3 cc (cubic centimeters) of blood for examination at the Health Laboratory Center for Makassar. From the examination result, 80 respondents had 100–125 mg/dL of fasting blood glucose. A total of 6 prospective respondents withdrew and the rest (n = 74) were assigned into two groups.

Data collection procedure

The research team visited the respondents who met the requirements to explain the research and obtain informed consent. After the prospective participants agreed, a randomization process for group determination was carried out. Capsules (extract and placebo) were given to the respondent once every 7 days, and the respondents' families were given a control card/card for taking medication companion to record consumption compliance. If extreme hypoglycemia occurred (<50 mg/dl), the respondent would be referred to the nearest hospital and claimed dropout [12]. At the first stage of the study, prediabetes/diabetes education was given and continued until the 4^{th} week. The education was provided face-to-face or in a small group if the family followed the COVID-19 health protocol.

Intervention material

A. altilis were taken from the Darul Istikoqoma Islamic boarding school in Timbuseng Village, Pattallassang District, Gowa Regency, Indonesia. After harvesting the fruit, a total of 50 kg old-yellow *A. altilis* were washed and cut into small pieces and then aerated to dry with avoiding direct sunlight [13]. *A. altilis* were then put in a room at 18°C for 3 × 24 h, mashed with a crusher, macerated with water 1:10 (for 3 h, stirring every 30 min. To separate the filtrate and residue, it used a spinner at 3000 rpm for 10 min. The filtrate was put into a freeze dryer at a temperature of −60°C so that the dry extract was solid and then put into capsules of size 00 with the weight of each dose was 500 mg [14].

Measurement of variables

During the study, we performed several measurements such as fasting blood glucose, using the enzymatic method is the enzyme glucose oxidase or hexokinase, which reacts with glucose, when blood is dropped on the test strip, the glucose catalyst will reduce glucose in the blood. The intensity of the electrons formed on the test strip is equivalent to the concentration of glucose in the blood, so that glucose levels can be measured. International Physical Activity Questionnaire is used to measure the level of physical activity in a research sample, this questionnaire has three scales: Low activity/walking, moderate activity and high intensity (vigorous) activity measured in the last 7 days, and food intake (24-h recall questionnaire).

Results

Characteristics of respondents

Most respondents in the intervention and control groups are women (68% vs. 76%). The highest age was 40–49 years (51.3% vs. 45.9%). The highest education level of respondents was high school (64.8% vs. 81.0%). The proportion of unemployed participants was high in both groups. Smoking status was almost 30% in the control group. There was no significant difference in characteristics between the intervention and the control groups (Table 1).

Changes in fasting blood glucose, physical activity, and dietary intake after intervention The analysis of the mean in the intervention group using the Wilcoxon test is that the results of pretest (Mean ± SD) 114.89 ± 6.6 and posttest (Mean ± SD) 98.73 ± 4.8 with p = 0.000. Because of $p < 0.05$, it was concluded that there was a significant difference in the pre-posttest intervention group while in the control group using the T-test, the results of the mean are pretest (Mean ± SD) 113.62 ± 6.6 and posttest (Mean ± SD) 113.59 ± 6.7 with p = 0.768. Because of $p > 0.05$, it can be concluded that there was no significant difference in the pre-posttest control group. Fasting blood glucose levels in the intervention group were significantly decreased after 28 days of intervention (−16.16 mg/dL) but not in the control group (−0.03 mg/dL). Changes between the intervention and the control group were significantly different between the two groups ($p < 0.001$) (Table 2).

Table 3 shows the changes in physical activity and dietary intake of the participants in both groups after 28-days of intervention. The result shows that physical activity (1312.13 ± 145.1 vs. 1350.9 ± 129.8, $p < 0.001$), energy intake (1590.86 ± 295.0 vs. 1825.09 ± 489.4, p = 0.03), and carbohydrate intake (251.82 ± 60.26 vs. 240.56 ± 80.28, $p < 0.001$) were significantly changed in the intervention group. Meanwhile, there were no changes in the control group for all variables.

Table 1: Characteristics of participants

Characteristics	Intervention group (n = 37)		Control group (n = 37)		p
	n	%	n	%	
Sex					
Male	12	32.0	9	24.0	0,439
Female	25	68.0	28	76.0	
Ages					
30–39 years	4	10.8	6	16.2	0.774
40–49 years	19	51.3	17	45.9	
50–59 years	14	38.9	14	38.9	
Level of education					
Elementary School	2	5.4	0	0	0.267
Junior High School	8	21.6	6	16.2	
Senior High School	24	64.9	30	81.1	
College/diploma	3	8.10	1	2.7	
Occupation status					
Employed	11	29.7	18	48.6	0.096
Unemployed	26	70.3	19	51.4	
Smoking history					
Smokers	7	18.9	11	29.7	0.278
Non-smokers	30	81.1	26	70.3	
Family history of DM					
Yes	20	54.0	27	72.9	0.091
No	17	46.0	10	27.1	

Discussion

The results showed that the level of fasting blood glucose decreased. The results of the Wilcoxon Signed-Ranks Test showed “there is a significant difference in the level of fasting blood glucose in the intervention group given *A. altilis* extract capsules, compared to the control group. This study is in line with the research that found that *A. altilis* extract could reduce blood glucose levels in rats with 100 mg/kg bb of *A. altilis* extract after exposure to 120 mg/kg of alloxan [15], [16]. The research conducted by Putu *et al.* (2015) with a dose of 100 mg/kg BW of *A. altilis* extract (ethanol) used rats for 21 days could reduce blood glucose levels by 66.77% [15].

The study conducted by Nurhaedar (2020) using a decoction of *Cinnamomum burmannii* (cinnamon bark) for 14 days showed the result that it could reduce fasting blood glucose in the intervention group by (−4.14 mg/dL) [8]. The result of the study from Mujianti *et al*. (2018) giving 250 ml of Moringa leaf tea to prediabetic women for 28 days could reduce fasting blood glucose (−13.42 mg/dL) [9].

In another study, several plants that can lower blood glucose include sweet potato leaves

Table 2: Changes in fasting blood glucose between the intervention and the control groups

Variable	Group	n	Pre Mean ± SD	Post Mean ± SD	p-value	Δ	p
Fasting blood glucose	Intervention	37	114.89 ± 6.6	98.73 ± 4.8	0.000**	−16.16	<0.001
	Control	37	113.62 ± 6.6	113.59 ± 6.7	0.768*	−0.03	

containing the main components, namely: flavonoids, glycoproteins, anthocyanins, and alkaloids studied by Akthar *et al*. (2018). *In vivo*, alloxan-induced Wistar rats then given sweet potato leaves for 14 days showed a decrease in blood glucose [17], [18]. A study conducted by Eka *et al*. (2019) employed an experimental design in which 15 Wistar rats were given papaya leaf extract 200 mg/kg BW orally using a gastric probe once a day for 14 days. The results showed a significant decrease in glucose compared to the control group [19]. This study is consistent with Venkateshwarlu *et al*. (2013), where papaya contains flavonoids, tannins, and alkaloids that have a hypoglycemic effect [20].

Table 3: Changes in physical activity and diets between the intervention and the control groups

Variable	Group	n	Pre Mean ± SD	Post Mean ± SD	p
Physical activity (Met)	Intervention	37	1312.13 ± 145.1	1350.9 ± 129.8	0.000**
	Control	37	1654.65 ± 199.3	1298.73 ± 156.2	0.053**
Energy (kcal)	Intervention	37	1590.86 ± 295.0	1825.09 ± 489.46	0.003*
	Control	37	1614.74 ± 294.6	1634.66 ± 379.60	0.800*
Protein (g)	Intervention	37	44.45 ± 16.69	46.78 ± 16.49	0.267**
	Control	37	43.96 ± 13.46	48.72 ± 13.99	0.126*
Fat (g)	Intervention	37	54.08 ± 28.01	49.18 ± 20.42	0.839**
	Control	37	51.64 ± 24.02	54.46 ± 24.69	0.573*
Carbohydrate (g)	Intervention	37	251.82 ± 60.26	240.56 ± 80.28	0.000*
	Control	37	252.44 ± 54.92	266.48 ± 71.46	0.297*

In this study, compared to other studies, they both contain flavonoid compounds but differ in the solvent and maceration method. Flavonoids are powerful antioxidants useful in reducing the adverse effects of oxidative stress that might cause diabetes. Good flavonoid antioxidants can lower blood glucose, which is the best treatment [21]. Flavonoids play a crucial role as natural antioxidants mainly to capture free radicals, such as hydroxyl radicals (OH), superoxide onions (O2−), peroxyl radicals (OOH). Antioxidant activity associated with phenolic OH groups can regenerate tissue or cells damaged by inflammation in the pancreas.

Flavonoids increase glycogenesis, which stabilizes blood glucose levels to remain normal, whereas flavonoids increase metabolic processes that convert glucose into glycogen in the liver. The hormone insulin activates this process. In addition, flavonoids inhibit enzymes associated with superoxide anion radicals such as protein kinase and xanthine oxidase and inhibit cyclo-oxygenase, glutathione S-transferase lipoxygenase, microsomal monooxygenase, mitochondrial succinate oxidase, and Nicotinamide Adenosine Dinucleotide Hydrogen oxidase. All of them are involved in the formation of reactive oxygen species (ROS).

The decrease in glucose levels into cells causes the conversion of fatty acids, amino acids from muscle tissue (from the breakdown of muscle protein) into glucose in liver cells through gluconeogenesis, resulting in hyperglycemia. Hyperglycaemia causes nicotinamide adenine dinucleotide phosphatase activation and suppression of oxidant enzymes increases and forms the accumulated ROS, causing oxidative stress. This oxidative stress process inhibits signals from insulin receptors by blocking the pathway between insulin receptor substrates and PI3K, so there is no translocation of GLUT 4 from intracellular to plasma membrane in which glucose uptake into cells decreases. This condition causes insulin resistance.

Hyperglycemia in prediabetes causes increased oxidative stress and decreased endogenous antioxidants (antioxidants produced by the body). Therefore, the body needs exogenous antioxidants. Exogenous antioxidants can be obtained by increasing the food intake containing antioxidants such as flavonoids, isoflavones, polyphenols, Vitamin A, beta carotene, Vitamin C. *A. altilis* (flavonoids) can prevent the development of prediabetes into type 2 DM because they have insulin-like activity [22].

This study used *A. altilis* extract by using the cold maceration method with water solvent without heating, which can damage the processed material [23]. Water is polar similar to flavonoids, and it is not toxic. This study is supported by Vongsangnak *et al*. (2004) stated that the heating process at an extraction temperature of 80ºC in saponin level tends to decrease. This is because the saponin compounds are oxidized, causing structural changes and decreasing levels of extracted compounds [24].

Extraction using water without heating is safer, and it avoids the risk of damaging compounds in thermolabile plants. Separation is based on differences in the distribution of the components contained in a substance or extract. The separation method is an essential aspect in analysis to obtain a good and quality compound.

The result of physical activity statistical in the intervention group was a significant increase while the control group did not change. Increased physical activity can regulate blood glucose. The magnitude of the effect of physical activity is very dependent on the intensity, duration, and type of activity besides other factors. The mechanism of the relationship between physical activity and the risk of prediabetes is that physical activity can improve energy balance and prevent obesity and other factors related to prediabetes [25], [26]. Physical activity can reduce blood glucose levels and increase insulin receptor sensitivity so that insulin hormone productivity is better and blood glucose levels decrease [27].

High energy intake increases the risk of prediabetes, diabetes, obesity, and cardiovascular diseases, etc. [28]. Energy balance could occur if the energy formed can be appropriately used according to the body's needs. In this study, the intervention group showed a significant increase in energy intake, while there was no significant difference in the control group before and after the intervention. This condition could occur due to multi-factors including education, habits, and income. High income plays a significant role in determining the increase in purchasing power, causing the increase in energy intake. In addition, snacking habits would also affect energy intake [29]. The fasting blood glucose in the intervention group decreased, although there was an increase in energy because *A. altilis* extract improved pancreatic function to reduce glucose.

There was no significant difference in protein intake in the intervention group before and after being given *A. altilis* extract capsules, while there was a significant difference in the control group before and after being given a placebo capsule. This condition indicates that protein intake does not directly affect blood glucose levels. This is in line with the study by Mirmiran (2017), who found that total dietary protein intake (RH = 0.13, 95% CI = 0.92–1.38) is not directly related to the occurrence of dysglycemia. However, there was a significant correlation in amino acids, such as higher glutamic acid and proline levels, with the risk of prediabetes [30].

Fat intake results showed no significant difference between the intervention and control groups before and after being given *A. altilis* extract capsules and placebo. Fat nutrition is a macromolecule that produces the highest energy compared to other macromolecules, 1 g of fat has nine calories. Low fat intake or <30% of total energy is recommended to prevent prediabetes, diabetes, and cardiovascular disease. This circumstance is expected to avoid the increase of fasting blood glucose in the intervention group.

Carbohydrate intake showed a significant decline in the intervention group before and after being given *A. altilis* extract capsules. In contrast, the control group had no significant difference before and after being given a placebo capsule. This condition is as expected, where respondents can control carbohydrate intake, which plays a role in maintaining blood glucose levels.

Conclusion

The result of the study is that giving *A. altilis* extract at a dose of 500mg twice a day for 28 days reduced prediabetes blood glucose by (−16.16 mg/dL).

Ethical Approval

Ethical approval for this study was granted by the Ethics Faculty of Public Health at Hasanuddin University, Makassar, Indonesia, number 7903/UN4.14./TP.02.02/2020 on June 15, 2020. Each respondent gave written consent during research registration.

Availability and Data Collection

The data used and analyzed during the study were at the author’s reasonable request data.

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