EVALUATION OF ASHITABA (*ANGELICA KEISKEI*) CRACKERS FORMULATIONS AS A-GLUCOSYDASE ENZYME INHIBITORS

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ABSTRACT

One of the global health issues is diabetes mellitus, characterized by elevated blood glucose levels. The absorption of glucose in the body occurs through the digestion of carbohydrates by the enzyme α-glucosidase, which is responsible for hydrolyzing carbohydrates into sugar. Ashitaba (Angelica keiskei) is a herbal plant from Japan and has long been utilized in traditional medicine for its various health benefits and preventive properties against multiple diseases. This plant has also been cultivated in Indonesia, including Trawas Mojokerto, East Java. This study aims to develop ashitaba crackers and evaluate their potential α-glucosidase inhibitory activity to develop safe and effective natural products to assist in managing diabetes more efficiently. This research was conducted from July to September 2022. Two formulations of fresh ashitaba leaves were used (12% CAST 1 and 18% CAST 2 of 100 g of flour). Based on the results of this research, chemical composition tests showed that the carbohydrate and dietary fiber content in CAST 1 were higher than those in CAST 2. Protein, lipid, water, and ash content in CAST 2 had higher values than in CAST 1. Flavonoid content and inhibitory activity test results of ashitaba crackers showed significant differences between the two formulation groups regarding flavonoid content and percentage inhibition against the α-glucosidase enzyme. Both flavonoid content and inhibitory activity in CAST 2 were higher than in CAST 1. Ashitaba crackers with the best formulation in this study, based on flavonoid levels and their ability to inhibit α-glucosidase enzyme, were identified as CAST 2.

Keywords: *Ashitaba Crackers, α-glucosidase inhibitor, flavonoids*

INTRODUCTION

Diabetes mellitus is a chronic disease often associated with various serious complications, including heart disease, kidney dysfunction, vision impairment, and nervous levels in the body system disorders (Cao et al., 2019). One of the global health issues is diabetes mellitus, characterized by elevated blood glucose. The primary approach to managing diabetes mellitus is controlling blood glucose levels.

The glucose absorption process in the body occurs through the digestion of carbohydrates by the enzyme α-glucosidase, which is responsible for hydrolyzing carbohydrates into simple sugars. This mechanism leads to an increase in blood glucose levels, especially after meals. Inhibitors of α-glucosidase (AGIs) from various plant sources are currently trending due to their ability to inhibit α-glucosidase activity, resulting in a reduction in the hydrolytic cleavage of non-reducing ends of dietary oligosaccharides and a diminished release of α-glucose. This inhibits carbohydrate digestion and glucose absorption in the small intestine. This mechanism plays a crucial role in controlling postprandial hyperglycemia, representing a modern therapeutic approach to stabilize blood glucose levels in diabetic patients, especially in type 2 diabetes (Hossain et al., 2020).

In recent years, there has been a growing interest in the use of natural substances as alternative treatments for diabetes. Ashitaba has emerged as one of the alternative herbal plants for prevention and therapy in controlling blood glucose in patients with diabetes mellitus. Previous research conducted by Fu et al. (2023) indicates the potential of ashitaba fermentation extract in obese rats to reduce blood glucose, improve glucose tolerance, and enhance insulin sensitivity.

Ashitaba (Angelica keiskei) is a herbal plant from Japan and has long been utilized in

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traditional medicine for its various health benefits and preventive properties against multiple diseases. This plant has also been cultivated in Indonesia, including Trawas Mojokerto, East Java. Ashitaba is characterized by its fresh green leaves with a finger-like shape. Belonging to the Umbelliferae family, it is also known as "Tomorrow's Leaf" due to its ability to regrow after harvesting. Angelica keiskei is rich in chalcones, flavonoids, coumarins, and other bioactive compounds. These active compounds seem responsible for ashitaba's potential in various biological activities, including anti-tumor, antioxidant, liver protection, antibacterial, and antiviral properties (Fu et al., 2023).

One form of ashitaba utilization in this study is in the form of ashitaba crackers. The development of ashitaba cracker products has the potential as a healthy snack alternative with additional benefits in controlling blood glucose levels and inhibiting α-glucosidase enzyme. Therefore, this research is aimed at the development of ashitaba crackers, the examination of flavonoid levels in the product, and the evaluation of the inhibitory capabilities of ashitaba crackers against the α-glucosidase enzyme. The expected outcome of this study is to provide a meaningful contribution to the advancement of products derived from natural and safe ingredients, demonstrating efficacy. Furthermore, these products hold the potential to aid the management of blood glucose levels and the prevention of hyperglycemia.

METHODS

The primary material utilized in this research was the ashitaba leaves derived from the ashitaba plant (Angelica keiskei), obtained from cultivation in the Trawas plantation, Mojokerto.

In this study, an experimental method was employed in the laboratory using a completely randomized design with two treatments, namely the administration of ashitaba leaves (CAST 1 = 12% and CAST 2 = 18% of the weight of the flour used) as the raw material for crackers. The experimental units conducted were the ashitaba crackers, which were further analyzed. Ashitaba crackers were processed in the Processing Laboratory of the Nutrition Study Program at UIN Sunan Ampel Surabaya. Chemical characteristic tests were conducted at the Saraswati Indo Genetech Laboratory in Bogor. Flavonoid content tests on Ashitaba crackers were performed at the Pharmacy Laboratory of Airlangga University. The inhibitory activity of the α-glucosidase enzyme was analyzed at the Tropical Biofarmaka Study Center Laboratory, IPB University.

The obtained data were processed using Microsoft Excel and SPSS. For the initial data, a normality test using the Shapiro-Wilk test was conducted for all chemical characteristic data, flavonoid content, antioxidant activity, α-glucosidase enzyme inhibitory activity, and sensory tests. If the obtained data were normally distributed, statistical analysis was then carried out using the T-test with a significance level of $p < 0.05$. Conversely, for non-normally distributed data, the non-parametric Mann-Whitney test was conducted.

Processing Ashitaba Crackers

The primary raw materials used for making ashitaba crackers in this study are sorghum flour and arrowroot starch, which have a lower glycemic index than wheat flour. Two formulations of fresh ashitaba leaves were added, namely 12% (CAST 1) and 18% (CAST 2) of 100 g of flour. Thus, both types of crackers share the same basic raw material formulation, and the difference lies in the added ashitaba leaves. The proportions of ashitaba leaves were chosen based on a study conducted by Ohnogi et al. (2012, where a significant reduction in BMI, visceral fat, and total fat was observed in pre-metabolic syndrome patients given 6.1 g of dried ashitaba flour.

The utilization of the mentioned formulation was adopted and modified from a study conducted by (Ohnogi et al., 2012), where there was a significant decrease in BMI, visceral fat, and total fat among patients prone to metabolic syndrome who were administered ashitaba powder twice a day, each time with a dosage of 3.1 g. Therefore, the full daily dosage of ashitaba powder was 6.2 g. This dosage was subsequently adjusted in the current research for the formulation of ashitaba crackers to be 12% and 18% (12 g and 18 g) of fresh leaves per 100 g of flour used, considering the potential nutrient loss during the processing.

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Table 1. Formulation of Ashitaba Crackers

Ingredients	Proportion of Ashitaba Leaves	
	CAST 1 (12%)	CAST 2 (18%)
Sorghum Flour (g)	70	70
Arrowroot Flour (g)	30	30
Sorbitol Sweetener (g)	2.5	2.5
Water (ml)	40	40
Olive Oil (g)	10	10
Butter (g)	20	20

Table 1 shows the components of ashitaba crackers formulated in this study.

The stages in the ashitaba crackers processing were obtained and modified (Cauvain, 2015), followed by preliminary research and the formulation conducted independently by the researcher. The first step in making ashitaba crackers is to crush fresh ashitaba leaves, which have been sorted and thoroughly washed, using a blender. Dry ingredients are mixed according to the formulation before being combined with wet ingredients such as margarine, water, and virgin olive oil. Once the dough is formed, the blended fresh ashitaba leaves are added and mixed. The next step involves molding the dough into portions, weighing 12 grams when wet. Subsequently, the crackers are baked at 160ºC for 20 minutes. The dry weight for each cracker after baking is 8 grams.

Generally, the process of making ashitaba crackers can also be observed in Figure 1.

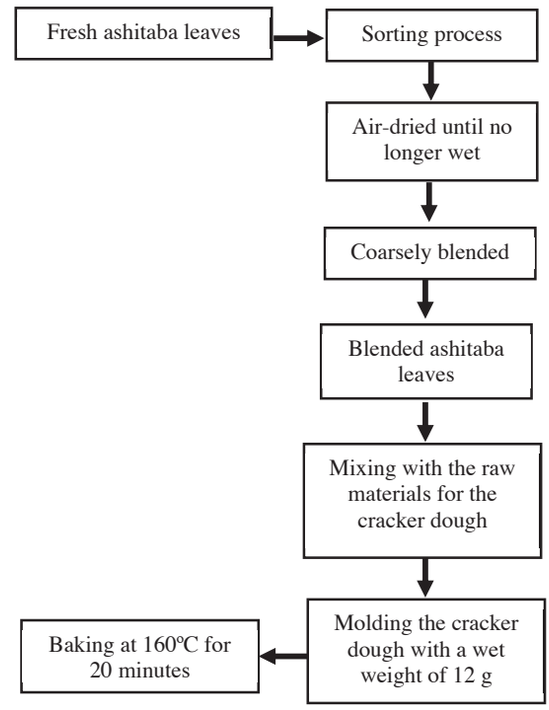

Figure 1. Ashitaba Crackers Manufacturing Procedure

Carbohydrate Analysis

The carbohydrate content was calculated using the by-difference method, which involves subtracting the sum of the four components, water content, protein, fat, and ash, from 100%.

Protein Analysis

The protein content analysis was performed using the titrimetric method. The protein content can be calculated using the formula derived from the titration results of the protein sample, as follows:

$$\text{Protein Content} = \frac{(A-B)\times N\times 0.014\times 6.25}{Weight\ of\ Sample} \times 100\%$$

Note:

A = ml of NaOH for blank titration; B = ml of NaOH for sample titration; N = Normality of NaOH.

Analysis of Lipid Content

The fat content analysis in this study was conducted using the Weibull method. A total of 2 grams of the sample was weighed using a beaker, then 30 ml of 25% HCl was added along with 20 ml of water and some boiling stones. The beaker was then covered and heated to boiling for approximately 15 minutes. Subsequently, filtration was carried out while hot until no more acid reaction occurred. Next, using filter paper dried in advance at 100-105°C, it was placed into a filter paper thimble and extracted with hexane or other fat solvents for 2-3 hours at approximately 80°C. The hexane solution was then distilled, the extracted fat was dried at 100-105°C, then cooled,

and the result was weighed. The drying process was repeated several times until a constant weight was achieved. The fat content was then calculated using the following formula:

$$\% \text{ Lipid Total} = \frac{W1-W2}{W} \times 100\%$$

Where:

W: Sample weight (g); W1: Fat flask weight after extraction (g); W2: Fat flask weight before extraction (g)

Water Content Analysis

The moisture content analysis in this study uses the SNI method. The initial step in this analysis involves weighing 1-2 g of the sample in a bottle with a lid, and the weight of the bottle is recorded. Subsequently, the sample is dried in an oven at 105°C for 3 hours. Once completed, the sample bottle is cooled in a desiccator to prevent moisture absorption from the surrounding air. Then, multiple weighings are performed until a stable or constant weight is obtained. The total moisture content is calculated using the following formula

$$\% \text{ Moisture Content} = \frac{W}{W1}\ x\ 100\%$$

Where:

W: Sample weight before drying (g); W1: Weight loss after drying (g)

Ash Content Analysis

Ash content analysis is conducted using the SNI method. The procedure involves weighing 2-3 grams of the sample into a known-weight porcelain crucible. It is then heated and incinerated in a muffle furnace at a maximum temperature of 500°C until complete incineration (occasionally, the furnace door can be slightly opened to allow oxygen to enter). The crucible containing the incinerated sample is cooled in a desiccator, then weighed several times until a constant weight is obtained. The percentage of ash content can be calculated using the following formula:

$$\% \text{ Ash Content} = \frac{W2-W1}{W} \times 100\%$$

Note:

W: Sample weight before incineration (g); W1: Weight of the sample + crucible after incineration (g); W2: Weight of the empty crucible (g).

Dietary Fiber Analysis

The analysis of dietary fiber is conducted using the enzymatic gravimetric method. The principle of the gravimetric method for dietary fiber involves determining the total soluble dietary fiber and insoluble dietary fiber. The first step is to weigh a sample of 15 g and place it in an Erlenmeyer flask. The sample is then added to 25 ml of 0.1 M sodium phosphate buffer pH six and stirred. Then, the thermal amylase enzyme is added and incubated for 15 minutes at 100°C and allowed to cool. The sample is then added to water to adjust the pH to 1.5, and then 100 mg of pepsin is added and incubated again at 40°C for 60 minutes. Next, the pH is adjusted to 4.5 with HCl and filtered using a crucible. The insoluble dietary fiber in the form of residue is then washed using 2x10 ml of 95% ethanol and 2x10 ml of acetone, followed by drying in an oven at 105°C and incineration at 550°C for 5 hours in a muffle furnace. The soluble dietary fiber in the form of filtrate is then adjusted to a volume of 100 ml, added with 95% ethanol, and allowed to settle for 1 hour. Then, it is filtered using a crucible and washed with 2x10 ml of 95% ethanol and 2x10 ml of acetone. It is then dried in an oven at 105°C and incinerated at 550°C for 2 hours in a muffle furnace. The calculation of dietary fiber content can be done using the following formulas:

$$\text{insoluble dietary fiber} = \frac{(K2-K1)-(C2-C1)}{W} \times 100$$

$$\text{Soluble dietary fiber} = \frac{(K4-K3)-(C4-C3)}{W} \times 100$$

Total dietary fiber = serat pangan terlarut + serat pangan tidak terlarut

Where:

K1: weight of empty filter paper (g); K2 : weight of filter paper residue (g); K3: Weight of empty filter paper (g); K4: Weight of filter paper filtrate (g); C1: Weight of empty crucible (g); C2: Weight of crucible residue (g); C3: Weight of empty crucible (g); C4: Weight of crucible filtrate (g); W: Sample weight.

Analysis of Total Flavonoid

In the analysis of total flavonoid compounds, sample preparation was conducted by first extracting ashitaba crackers using the maceration method with 70% ethanol as the solvent. After extraction, the liquid sample was then analyzed using the spectrophotometer method.

A 10 µL solution of the ashitaba cracker extract was placed into a 96-well transparent polystyrene microplate, followed by the addition of 120 µL distilled water, 10% aluminum chloride (10 µL), 1 M potassium acetate (10 µL), and absolute methanol (60 µL). The mixture was then incubated at room temperature for 30 minutes. Absorbance was measured using a microplate reader at a wavelength of 415 nm. A calibration curve was prepared using a quercetin standard solution with concentrations of 100, 200, 300, 400, and 500 ppm following the same procedure. Total flavonoids were expressed in quercetin equivalents (mg QE/g) using the equation:

$$C = \frac{c \times FP \times V}{m}$$

Where: C = Total flavonoids (mg QE/g); c = Flavonoid concentration (mg/L); DF = Dilution factor; V = Sample volume (L); M = Sample weight (g)

Analysis of α-Glucosidase Enzyme Inhibition

The α-glucosidase enzyme inhibition assay was conducted using the spectrophotometer method. Ten µL of 0.1 U/mL α-glucosidase (yeast maltase, dissolved in 0.2 M PBS, pH = 6.8) was added to each well of a 96-well plate containing 0.2 M PBS (pH = 6.8) up to a total volume of 150 µL. The solution mixture was then incubated in the dark at 37ºC for 10 minutes. Subsequently, 50 µL of 3 mM PNPG (4-nitrophenyl α-D-glucopyranoside) was added to each well and incubated at 37ºC for 10 minutes. Following this, 50 µL of 1 M Na2CO3 was added. The solution with 50 µL of 1 M Na2CO3 added before PNPG served as the blank, and PBS without the sample was used as the control. Acarbose was used as the positive control. Optical density was then measured at a wavelength of 405 nm. The α-glucosidase inhibition was calculated using the following formula:

$$Inhibitory\ rate\ \% = \frac{(ODc - ODcb) - (ODs - ODsb)}{ODc - ODcb} \times 100\%$$

OD represents the absorbance of the sample, Odsb is the absorbance of each sample, Odc is the absorbance of the control, and Odcb is the absorbance of the blank control (Luo et al., 2012).

RESULTS AND DISCUSSIONS

Crackers are a popular snack due to their likable taste, long shelf life, and relatively affordable price (Nicole et al., 2021). Healthy foods that contain fiber, antioxidants, low sugar content, and appropriate fat content contribute to maintaining blood glucose and preventing diabetes complications (Njapndounke et al., 2021). Figure 3 below shows the resulting ashitaba crackers from these two formulations.

The formulation of crackers in this study uses the main ingredients of sorghum flour and arrowroot starch, which are gluten-free and have a low glycemic index. Additionally, the primary focus of this research is the incorporation of ashitaba leaves as a crucial ingredient expected to contribute to the development of healthy crackers.

Chemical Characteristics Analysis

Crackers are products made from dough containing yeast or not, through fermentation or not, with low-fat content, generally without adding sugar, and typically have high moisture content (Cauvain, 2015).

Based on Table 2 of the formulations for the two types of ashitaba crackers, there is a significant influence on the proximate nutrient content ($p<0.05$). The carbohydrate and dietary fiber content in CAST 1 is higher than in CAST 2, at 64.57±0.67% and 7.19±0.065%, respectively. Meanwhile, the protein content (7.49%±0.048%), fat (22.98±0.53%), water content (6.29±0.139%), and ash content (2.71±0.066%) show higher values in CAST 2 compared to CAST 1. The protein content in ashitaba crackers has met the Indonesian National Standard (SNI), which specifies a minimum protein content of 5% for crackers. The

Table 2. Results of Chemical Characteristics Analysis of Ashitaba Crackers

Parameters	CAST 1 (%)	CAST 2 (%)
Carbohydrates	65.01	60.80*
Protein	7.31	7.28
Lipid	19.33*	22.91
Water Content	5.40*	6.35
Ash Content	2.96*	2.67
Dietary Fiber	7.16*	6.28

Note: (*) indicates significant difference (p<0,05)

higher water content in CAST 2 is suspected to arise from the difference in the amount of fresh ashitaba leaves added to the dough. Additionally, water is added to the dough during the production of both formulations. The difference in water content of the crackers can also be observed in crackers with 100% wheat flour as the main ingredient without any substitutions, which has a lower water content of 3.94% (Seftiono et al., 2019). However, the moisture content in dry foods such as biscuits, according to SNI 2973-2011, is maximally set at 5% (BSN, 2011). Nevertheless, when compared to other gluten-free cracker products, as seen in the study on cladode flour crackers by Dick et al. (2020), which falls within the range of 6.43-7.39%, the moisture content in the current research's ashitaba crackers, especially in the CAST 2 formulation, appears to exceed the recommended limit. Another study by Rico et al. (2019) on the moisture content of teff cereal crackers showed a range of 11.8% for brown teff crackers, 12.47% for white teff, and 8.32% for crackers formulated with rice.

Analysis of Total Flavonoids and α-Glucosidase Enzyme Inhibition

The results of the analysis of the inhibitory activity against the α-glucosidase enzyme in this study are expressed as the percentage of inhibition. In contrast, the flavonoid content is expressed in mg/g. The statistical test results in Table 3, using the T-test for flavonoid content and inhibition percentage of ashitaba crackers, indicate a significant difference between the two formulation groups regarding flavonoid content and the inhibition percentage against the α-glucosidase enzyme. Both flavonoid content and inhibition

Table 3. The Influence of Different Formulations of Ashitaba Crackers on Flavonoid Content and α-Glucosidase Enzyme Inhibition Activity

Formulation	Flavonoid (mg/g)	Inhibition Activity (%)
CAST 1	0.275 ± 0,050	0,045 ± 0,001
CAST 2	0.550 ± 0,057	0,271 ± 0,006
p-value	0.00*	0.00*

Note: (*) Indicates a significant difference (p < 0.05)

activity in CAST 2 are higher than in CAST 1, with values of 0.550 ± 0.057 mg/g flavonoid and 0.271 ± 0.006% inhibition against the α-glucosidase enzyme, respectively.

Based on the results of the analysis, it is also evident that the higher the flavonoid content in the cracker formulations, the higher the inhibition percentage. This result suggests that the inhibitory activity of ashitaba crackers is likely due to the presence of flavonoid compounds derived from adding ashitaba leaves. This is in line with the results conducted by Luo et al. (2012) in the analysis of compounds present in ashitaba extract using PNPG (4-nitrophenyl α-D-glucopyranoside) as a substrate that releases p-nitrophenol through hydrolysis by α-glucosidase enzyme; the study identified eight flavonoid derivative compounds exhibiting excellent inhibitory activity against α-glucosidase compared to the acarbose control. Over 100 types of bioactive compounds in ashitaba, including flavonoids, coumarins, phenolic compounds, acetylenes, sesquiterpenes, diterpenes, and triterpenes, have been identified (Kil et al., 2017). Flavonoid compounds in ashitaba, such as quercetin and isobavachalconere, are known for their effective inhibitory activity against glucosidase enzymes (Luo et al., 2012).

Enzyme α-glucosidase plays a crucial role in the catabolism of starch, glycogen, and disaccharides in the digestive tract. One way to control blood glucose levels is by inhibiting the activity of this enzyme, leading to a reduction in the carbohydrate metabolism rate in the intestines. The enzyme acts on the α-1,4 glycosidic bond, breaking down starch and disaccharides into glucose. Inhibiting this enzyme is essential for lowering blood glucose levels after meals, making

it a valuable target for diabetes management (Magaji et al., 2020).

The study conducted by Ohkura et al. (2018) reveals that leaves, stems, and roots of ashitaba contain various nutrients such as vitamin A, vitamin K, dietary fiber, and bioactive compounds, including chalcone, flavonol, and coumarin. Maronpot (2015) as well as Caesar and Cech (2016) assert that ashitaba powder contains several types of chalcone flavonoid compounds, with the most physiologically active compounds being 4-hydroxyderricin and xanthoangelol. These chalcone flavonoid compounds are known for their antioxidant, anti-inflammatory, anti-angiogenic, anti-diabetic, and anti-obesity properties.

Based on the flavonoid content in ashitaba, it is suspected that these flavonoids play a role in the regulation of blood glucose by inhibiting both alpha-glucosidase and alpha-amylase enzymes. In the treatment of diabetes mellitus, inhibition of enzymes responsible for the absorption and metabolism of carbohydrates, such as α-amylase and α-glucosidase, can be performed. These enzymes work in the absorption of glucose in the intestine. Inhibiting the breakdown of carbohydrates due to the action of these enzymes can prevent the postprandial increase in blood glucose levels (Kabré et al., 2023).

CONCLUSION

Ashitaba crackers have the potential to be developed as a healthy alternative snack, especially in efforts to prevent hyperglycemia and complications of diabetes mellitus. The results of this study show favorable proximate levels in ashitaba crackers. Additionally, ashitaba crackers contain flavonoids and exhibit inhibitory activity against the α-glucosidase enzyme, as demonstrated in in vitro tests, although further testing is required for conclusive findings.

The limitation of this research is the absence of a comparison between ashitaba crackers made from ashitaba leaf extract to assess various proximate nutrient characteristics, flavonoid levels, and the inhibitory capability against the α-glucosidase enzyme. A suggestion for future research is to create different formulations using ashitaba leaf extract and alternative low glycemic index flour types for further comparison.

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