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Research Article

In Vitro and In Vivo Anti Hyperglycemic Evaluation of *Sterculia quadrifida* Bark through The Inhibition of Alpha Glucosidase

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ABSTRACT

Data from the International Diabetes Federation revealed annual increases in the prevalence of diabetes mellitus, which require special attention. Implementation of the 'back to nature' trend presents opportunities to overcome this problem. As a medicinal plant, Faloak is widely used by people in Nusa Tenggara Timur, Indonesia. This study aimed to evaluate in vivo and in vitro anti-hyperglycemic activity of the bark of *Sterculia quadrifida*, known as Faloak. In vivo evaluation used sucrose-induced male mice. Measurements of glucose level employed a glucometer and data were analyzed statistically. Demonstrating anti-hyperglycemic activity of the bark of Faloak decoct, results showed doses 1.67 and 3.3 g/kg BW reduced glucose levels by 62.2% and 56.9%, respectively. In vitro examination of Faloak decoct at various concentrations used alpha glucosidase (sucrose) enzymatic reaction. Results of in vitro examinations demonstrated of Faloak bark decoct inhibited alpha glucosidase (sucrose) activity by 42.09 ± 4.39%. Further testing on humans is needed to confirm these findings.

INTRODUCTION

Diabetes as a chronic condition is characterized by high blood glucose levels (hyperglycemia) (WHO, 2019). Hyperglycemia over a long time period can cause serious complications which lead to death (Skyler *et al.*, 2017; Kottaisamy *et al.*, 2021). Accordingly, diabetic patients need immediate and effective treatment to control their glycemic index with HbA1c <6.5, eight-hour fasting plasma glucose (FPG) ≤ 126 mg/dl, and 2-hour plasma glucose during an oral glucose tolerance test ≤ 200 mg/dl) (International Diabetes Federation, 2019; Kim et al., 2019). There are many types of hyperglycemic drugs in the market (Marín-Peñalver *et al.*, 2016; Thrasher, 2017). For all patients with diabetes mellitus (DM), hyperglycemic treatment needs to consider efficacy, risk of hypoglycemia, effect on weight, side effects, and costs (Mosenzon *et al.*, 2016). One of the hyperglycemic drugs that meets these criteria is the alpha glucose inhibitor (AGI).

International Diabetes Federation recommends AGI as the treatment for patients with type II DM. The use of AGI is appropriate for first-, second-, third-line treatments and can be combined with other diabetes drugs (International Diabetes Federation, 2019). Several AGIs have been used in diabetic treatment, such as: Acarbose (Zhou *et al.*, 2012), Miglitol (Sugimoto *et al.*, 2015), and Voglibose (Kato *et al.*, 2020). Treatment with AGIs is known to control blood glucose levels by inhibiting alpha glucosidase enzymes to hydrolyze carbohydrates that delays its absorption (Laube, 2002). These conditions improved glycemic control of diabetic patients which was indicated from lower level of post prandial glucose (PPG), HbA1C and insulin (Cai *et al.*, 2013; Joshi *et al.*, 2015; Alssema *et al.*, 2021). Adverse effects of using AGI were gastrointestinal disorders, including flatulence, diarrhea and abdominal pain (Abe *et al.*, 2011). Those adverse effects caused a lack of adherence in scheduled treatment of diabetic patients to take AGI regularly. Therefore, the researchers quested for AGI substances from natural products which

are expected to have no adverse reactions such as those experienced with synthetic AGI.

Several natural products have activity as alpha glucosidase inhibitors. Saponin compounds which were isolated from *Polycias fruticose* leaves demonstrated activity as AGIs (Luyen *et al*., 2018). Dichloromethane extract of *Croton bonplandianum* Bill demonstrated activity as an AGI with IC_{50} 14.93 mg/mL (Qaisar *et al*., 2014). Ethyl acetate extract from *Borassus flabellifer* Linn and its isolated compounds demonstrated alpha glucosidase inhibition (Dej-adisai *et al*., 2017). Several ethanol extracts of leaves and twigs of some plants from *Clusiaceae*, *Apocynaceae*, *Rubiaceae*, and *Euphorbiaceae* had activity with range of IC_{50} (2.33-112.02 µg/mL) better than acarbose (IC_{50} 117.20 µg/mL) as AGIs (Elya *et al*., 2012). In vitro evaluation from ethyl acetate fraction of methanol extract of *Cornus capitate* leaves demonstrated alpha glucosidase inhibition better than acarbose (Bhatia *et al*., 2019). Norathyriol is an active metabolite of Mangifera in the human intestines and had activity to inhibit alpha glucosidase activity. This compound had better activity than Mangifera and acarbose and significantly reduced FPG (Shi *et al*., 2017). Caffeic acid and kaempferol which were obtained from ethanolic extract of lemongrass were responsible for inhibition of alpha glucosidase activity (Gunawan-Puteri *et al*., 2020). The potency of active compounds which were present in those plants to inhibit alpha glucosidase activity encouraged the researchers in the present study to discover a new compound in other plants as a natural source of AGIs.

Faloak (*Sterculia quadrifida*) is an indigenous plant which grows on the island of Timor, Indonesia and has been used empirically to treat many types of diseases. Faloak's bark contains flavonoids, tannins, terpenoids, and saponins (Dongga *et al*., 2016; Fernandez *et al*., 2017; Munawaroh *et al*., 2018). Several studies revealed that ethanol extracts from Faloak's bark decreased glucose levels in male white rats induced by alloxan and in male mice induced by glucose (Dongga *et al*., 2016; Fernandez *et al*., 2017). Therefore, this study aimed to evaluate the anti-hyperglycemic activity of Faloak's bark in vivo and in vitro. The selection of decoct was made in dosage form due to we wanted to extract the polar compounds contained in the plant. These were based on the compound's structure which had been proven as an AGI having polar property.

METHODS

Male DDY mice (2-3 months, 18-25 g) were obtained from Imono Laboratory of the Faculty of Pharmacy, Sanata Dharma University, Indonesia. Faloak (*Sterculia quadrifida*) bark was obtained from Nusa Tenggara Timur, Indonesia. The plant material was authenticated by the Herbal Garden Laboratory of Faculty of Pharmacy Sanata Dharma Univeristy with number 623/LKTO/FarUSD/IX/2021. Glucose, sucrose, *p-nitrophenyl-α-D-glucopyranoside* (PNPG), Sodium carbonate, phosphate buffer pH 7, *α-glucosidase*, Dimethyl sulfoxide (DMSO) that used in this study were of analytical grade and obtained from E-Merck (Darmstadt, Germany). Acarbose were produced by Dexa Medica, PT. Additional items included a glucometer strip, glucometer Accu-check®, and spectrophotometer UV-Vis (Shimadzu 1800).

Preparation of Faloak bark decoct

Dried bark of Faloak was powdered using a miller and sieved. The fibrous part was omitted. Ten g of Faloak powdered and 100 mL distilled water were stirred thoroughly, heated at 90°C for 30 min in an enamel pan then shaking constantly every 5 min. The mixture was filtered while hot using cheese cloth to obtain Faloak bark decoct with a volume of 100 mL.

In vitro alpha glucosidase inhibition test

Testing of the alpha glucosidase inhibitory activity of the Faloak bark decoct was conducted according to Gunawan-Puteri *et al.* (2010) with slight modification. To produce rat intestinal glucosidase, 0.1 g intestinal acetone powder was dissolved in 2 mL of EDTA 5mM until homogenous using cold mortar and pestle, then centrifuged at 11,000 rpm 4°. The supernatant was recovered and stored on ice. It was considered as rat intestinal glucosidase possessing activities to hydrolyze sucrose.

Each sample was tested for alpha-glucosidase inhibition activity 3 times (triplo). First, 25 µL of sample solution was added into 2 mL microtubes to sample and sample blank, while 25 µL of 50% DMSO was added to the control and control blank. Then 125 µL of substrate solution (21.90 mg/mL sucrose in 50% DMSO for sucrase inhibition assay) was added to each tube and agitated with vortex. Mixture was pre-incubated at 37 °C for 5 min with a water bath. Next, 100 µL of rat intestinal glucosidase solution was added to sample and control tubes, and the blanks were added with 100 µL of potassium phosphate buffer (0.1 M, pH 6.9). Mixture was incubated at 37 °C for 25 min. Each tube was then added with 750 µL of Tris-HCl solution (121.15 mg/mL of tris(hydroxymethyl)aminomethane in deionized water, pH 7). All of the mixtures were then passed

through a short aluminum oxide column made from shortened Pasteur pipette, cotton and 1 cm of aluminum oxide. Then, the filtered mixture was taken (30 µL for sucrose inhibition assay) and mixed with 200 µL of glucose CII test-kit Wako® solution in a 96 well plate and was left for incubation at 37°C for 5 min. The optical density of the wells was measured at 505 nm. Glucosidase inhibitory activity was evaluated based on inhibition against sugar hydrolysis and calculated using the Equation (1) below:

$$\% \text{ Inhibition} = \frac{(A_{\text{control}} - A_{\text{control blank}}) - (A_{\text{sample}} - A_{\text{sample blank}})}{(A_{\text{control}} - A_{\text{control blank}})}$$

where A stands for absorbance. A ' sample' is the absorbance value in the presence of Faloak, 'A control' is the absorbance value of a control reaction where Faloak is omitted. Reaction blanks were prepared by replacing intestinal acetone powder with sodium phosphate buffer.

In vivo anti hyperglycemic test

Normal healthy mice fasted overnight, were randomly divided into six groups of five mice each and received treatment orally. The oral sucrose tolerance tests (OSTT) for nondiabetic rats were performed according to the standard method. In short, Group I as normal control group, received aquadest. Group II was given acarbose (40 mg/kg BW). The doses of 0.8, 1.67 and 3.3 g/kg BW of Faloak bark decoct were administered to the Groups III, IV and V, respectively. All of the animals were given sucrose, at a dose of 4 g/kg BW.

Serum glucose of blood sample from tail vein was estimated by using glucometer at 0 (before treatment), 15, 30, 60, 90 and 120 min after the sugar challenge (Wulandari, 2016; Togashi *et al.* 2016; Fransisca *et al.*, 2018). A glucose tolerance curve was plotted and the trapezoidal rule was used to determine the area under the curve (AUC) (Shi *et al.*, 2017; Wahyuningsih *et al.*, 2018).

Table 1. Percentage of reduction of AUC of Faloak bark decoct in mice-induced sucrose orally (n=5)

Treatment	AUC (mg.minute/dL)	% AUC decrease
Normal control	10,956.0 ± 703.7 [a]	-
Sucrose control 4 g/kg	18,466.5 ± 496.4[b]	-
Acarbose + sucrose	14,526.0 ± 428.5[a,b]	52.5
Faloak decoct 0.8 g/kg + sucrose	16,465.5 ± 1186.9[b]	26.6
Faloak decoct 1.67 g/kg + sucrose	13,798.5 ± 1050.9[a,b]	62.2
Faloak decoct 3.3 g/kg + sucrose	14,196.0 ± 1810.2[a,b]	56.9

Notes: The results were presented in average ± standard deviation; a: $p<0.05$ vs sucrose; b: $p<0.05$ vs normal; AUC: Area Under the Curve.

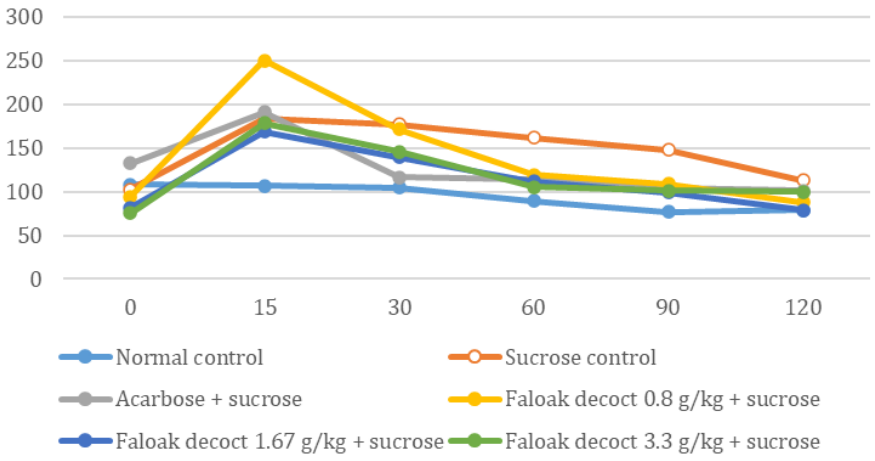

Figure 1. Blood glucose levels after 4 g/kg sucrose administration in normal mice.

Statistical Analysis

AUC values were analyzed using SPSS 22 software (IBM Corp., Armonk, NY). Using percentages with standard deviation (SD), a *p*-value <0.05 was considered statistically significant.

RESULTS AND DISCUSSION

The study aimed to evaluate in vitro and in vivo anti hyperglycemic activity of Faloak bark decoct. This study was approved by the Medical and Health Research Ethics Committee of the Faculty of Medicine, Public Health and Nursing, Universitas Gadjah Mada, Yogyakarta, Indonesia with number KE/FK/0274/EC/2021. We employed the sucrose inducing method to increase the glucose level of the mice. Glucose level measurements were made at 0-120th minutes after sucrose administration orally. In vitro anti hyperglycemic test was done by measuring alpha glucosidase activity.

The results of the in vivo study demonstrated that the sucrose control group had an increase in glucose level at the 15th min compared to 0th min, as shown in Figure 1. This condition indicates the mice were at the hyperglycemic level due to induction of sucrose. Increasing blood glucose levels in these mice were in accordance with several studies that indicated there was an increase blood glucose level in normal individuals after sugar administration orally (Gunawan-Puteri *et al*., 2020; Hendra *et al*., 2021). Other studies have reported an increase in glucose level of mice at 15 min after 4 g/kg sucrose administration (Poovitha *et al.*, 2016; Gunawan-Puteri *et al*., 2018).

Figure 1 shows the reducing glucose levels at the 30th until 120th min after glucose administration orally in all groups of mice, including: acarbose controls and all dose levels of treatment of Faloak bark decoct. Acarbose had anti-hyperglycemic agency by inhibiting alpha glucosidase activity. The inhibition occurred due to acarbose binding with alpha glucosidase that delayed carbohydrates from hydrolyzing to glucose. This mechanism reduced PPG. Acarbose treatment resulted in significantly lowering AUC value as much as 52.5% (AUC value 14,526.0 ± 428.5 mg.min/dL) compared to sucrose level, as displayed in Table 1. Value of AUC of acarbose control demonstrated a significant difference to normal controls. This result means that although there was a decrease in glucose level or anti-hyperglycemic agency due to acarbose administration in sucrose-induced mice but it was not equivalent to normal conditions. This finding was supported by another study which reported acarbose ability to reduce AUC value significantly compared to the glucose control group (Luyen *et al*., 2018). Additionally, inhibitory activity of acarbose against increases in glucose levels induced by the ingestion of sucrose by interfering with alpha-glycosidase activity in silkworms as well as in mammals (Matsumoto *et al*., 2016). Previously, it has been reported that acarbose may enhance glucose metabolism in mice by promoting the proliferation of islet β-cells and inhibiting PDX-1 methylation in islet β cells (Zhou *et al*., 2021).

It was observed that there was no significant (p>0.05) difference in AUC (16,465.5 ± 1,186.9 mg.min/dL) between the mice treated with 0.8 g/kg Faloak bark decoct when compared with sucrose. This finding implied that this dosage had no significant effect on lowering the blood glucose level in mice induced by sucrose orally. Means of AUC value of decoction of Faloak bark at doses of 1.67 and 3.3 g/kg BW were 13,798.5 ± 1,050.9 and 14,196.0 ± 1,810.2 mg.min/dL, respectively. These AUC values showed significantly difference (p<0.05) compared to sucrose and normal controls. They demonstrated the decoction of Faloak bark's ability to reduce glucose level in sucrose-induced mice by 62.2 and 56.9%, respectively but its reducing level was still unequal to normal conditions. In general, decoct of Faloak bark at doses of 1.67 and 3.3 g/kg BW had anti hyperglycemic activity in orally sucrose-induced mice. These findings also consistent with the study conducted by Dongga *et al*. (2016) that used ethanolic bark of Faloak on alloxan induced diabetic rat models. Fernandez *et al.* (2017), revealed that the ethanolic extract of Faloak's bark produced blood sugar reduction effects on oral glucose load in normal mice.

It has been established that blood glucose levels are highly affected by the saccharides contained in food which are converted into glucose by the actions of digestive enzymes such as alpha glucosidase. Sucrose as carbohydrates, are hydrolyzed to monosaccharides by alpha glucosidase which thereafter causes an increase in blood glucose. Therefore, it is more relevant to evaluate inhibitory activity of alpha glucosidase, where the major carbohydrates are disaccharides. In this study, a mammalian source of the digestive enzymes, alpha glucosidases which are structurally and mechanistically closely related to human enzymes was used for in vitro inhibitory assay (Laoufi *et al*., 2017). It was observed that decoct of Faloak bark exhibited 42.09 ± 4.39% (n=3) inhibitory activity at 50 mg/mL. This finding

confirms that decoct of Faloak bark had activity as an inhibitor of alpha glucosidase.

Faloak bark extracts contain various bioactive compounds which are recommended as a plant source of phytopharmaceutical importance (Siswadi *et al.,* 2021). It has been found previously that ethanol extracts from Faloak's bark contain flavonoids, tannins, terpenoids, and saponins (Fernandez *et al.*, 2017; Munawaroh *et al*., 2018). Many of the previous studies provide a series of potentially effective flavonoids that can be used as alternatives to exhibit inhibitory effects against alpha-glucosidase enzymes (Proença *et al*., 2017; de Oliveira *et al*., 2018; Borgesa *et al*., 2021).

The decoction of Faloak bark seems to delay the rapid digestion of sucrose, thus, lengthening the time needed for carbohydrate absorption. Flavonoids or some other unknown compounds in the decoct might be responsible for this reduction in the blood glucose levels of the normal rats. The tendency of the Faloak bark decoct to suppress the increase in blood glucose levels suggests the involvement of alpha glucosidase inhibiting activities observed in vitro.

CONCLUSIONS

In vivo study of Faloak bark decoct demonstrated its anti-hyperglycemic activity. Decoct of Faloak bark at doses of 1.67 and 3.3 g/kg BW were able to decrease glucose level by 62.2% and 56.9%, respectively. The in vitro study which was done by measuring alpha glucosidase activity demonstrated the decoct of Faloak bark had inhibiting activity against alpha glucosidase by 42.09 ± 4.39%. Based on both studies, we elucidated the anti-hyperglycemic activity of Faloak bark decoct through the mechanism of inhibiting alpha glucosidase activity.

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CONFLICT OF INTEREST

The authors declare there are not conflict of interest.

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