Pharmaciana
Vol.14, No.3, Nov 2024, Page. 289-298
ISSN: 2088 4559; e-ISSN: 2477 0256
DOI: 10.12928/pharmaciana.v14i3.28263

In vitro and *in vivo* anti-hyperglycemia effects of extract of Faloak (*Sterculia quadrifida* R.Br.) leaves

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Submitted: 22-01-2024 ***Reviewed: 23-09-2024*** ***Accepted: 18 -11-2024***

ABSTRACT

Despite the availability of various conventional treatments, diabetes mellitus remains a serious global health concern with an increasing prevalence. This trend underscores the need to explore potential natural alternatives. Faloak, an indigenous plant of Indonesia, has been traditionally used for various health conditions, yet its potential as an anti-hyperglycemic agent has not been comprehensively investigated. This research focused on identifying the ingredients of Faloak leaves that could lower blood sugar levels and confirm these effects in laboratory and animal models. At various concentrations, the *in vitro* evaluation assessed the inhibitory effect of α-amylase and α-glucosidase enzymes. For *in vivo* evaluation, male mice were administered glucose, sucrose, and starch after being pretreated with Faloak leaf extract, and their blood glucose levels were monitored for 120 min. Faloak leaf extract demonstrated significant inhibitory activity against α-amylase and α-glucosidase enzymes. The IC_{50} values for sucrose and maltose inhibition were 30.37 and 65.36 mg/mL, respectively, while α-amylase inhibition showed an IC_{50} of 27.02 mg/mL. In the in vivo test, mice pretreated with the extract exhibited significantly decreased blood glucose levels at 120 min compared to the control group. These findings indicate that the ethanolic extract of Faloak leaves possesses promising anti-hyperglycemic activities, positioning it as a potential candidate for developing plant-based blood glucose management. Our results demonstrate that Faloak leaf extract exhibits substantial anti-hyperglycemic properties, inhibiting vital digestive enzymes and effectively reducing postprandial glucose levels. Identifying active ingredients paves the way for further research to elucidate specific bioactive compounds and their mechanisms of action.

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Keywords: glucose; sugar; starch; glucosidase; amylase; *Sterculia quadrifida*

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INTRODUCTION

High blood sugar, or hyperglycemia, can indicate diabetes and other health problems (Perkumpulan Endokrinologi Indonesia, 2021). Long-term hyperglycemia increases the risk of liver, kidney, and heart impairment in patients with diabetes mellitus (American Diabetes Association, 2022). The International Diabetes Federation estimates that the number of adults with diabetes is expected to rise from 643 million in 2030 to 783 million by 2045. Furthermore, because of impaired glucose tolerance, around 500 million people are more likely to acquire type 2 diabetes (International Diabetes Federation, 2021).

A "back to nature" lifestyle is currently popular in Indonesian society, where medicinal plants are used to preserve and improve health. The genus Sterculia includes the common medicinal plant Faloak (*Sterculia quadrifida* R. Br.) found in the East Nusa Tenggara area. According to a previous study, various types of Sterculia were historically employed to address various health issues such as microbial infections, diabetes, skin conditions, gastrointestinal disorders, inflammation, and more. The Sterculia plant has been used in many countries for diverse traditional and medicinal purposes, from roots to leaves. They have been utilized for the treatment of different conditions like skin problems, gastrointestinal disorders, diabetes, and respiratory ailments (El-Sherei et al., 2016; Rollando et al., 2020; Siswadi et al., 2014; Susanto, 2019).

Studies have shown that Faloak bark exhibits an in vivo anti-hyperglycemic activity (Fernandez & Edel, 2017; Julianus et al., 2023). This activity is made possible by the secondary metabolites found in Faloak bark, which include tannins, phenols, steroids, and flavonoids. The community's harvesting of Faloak bark often exceeds the plant's ability to regenerate bark. The continued exploitation of Faloak bark raises concerns about the potential depletion of Faloak plants. Therefore, research into the Faloak's other components, particularly its leaves, is crucial for practical use and conservation.

Radjah et al. (2021) discovered that both Faloak leaves and bark contain similar secondary metabolites, such as phenols, tannins, steroids, and flavonoids (Dillak et al., 2019; Siswadi & Saragih, 2021). Despite this, the anti-hyperglycemic effects of Faloak leaf extract have not been studied. The purpose of this study was to find out whether the extract could lower blood sugar levels. Furthermore, to determine the component (s) responsible for the pharmacological activity, the active ingredients of the Faloak leaf extracts were identified, and the anti-hyperglycemic effect was also assessed through in vivo and in vitro studies.

MATERIALS AND METHOD

Materials

Dried Faloak leaf Simplicia was collected from Kupang, East Nusa Tenggara, in March 2022 and identified by experts from the Biologic Department of Sanata Dharma University. The study utilized ethanol, glucose, sucrose, starch, p-nitrophenyl-α-D-glucopyranoside, phosphate buffer pH 7, DMSO, α-glucosidase, and sodium carbonate, all of which were procured from E-Merck.

Methods

Preparation of ethanol extract from Faloak leaves (EEF)

Dried Faloak leaf simplicia was powdered and macerated using 70% ethanol for 24 hours with a ratio of 1:10. The mixture was filtered, and then it was concentrated at 40°C in a rotary evaporator to extract the active components (Tzanova et al., 2020; Zhang et al., 2018). The crude extract was stored in a dark glass bottle at four °C.

Qualitative phytochemical screening

Standard assays were used to perform a phytochemical screening of the plant under study to determine the presence of active principles. Table 1 shows standard screening tests were carried out to determine whether secondary metabolites were present or absent.

Table 1. Tests for phytochemical screening of ethanol extract from Faloak leaves

Tests	Reagent	Color appearance	Inference	References
Flavonoid detection	Extract + magnesium + HCl	Pink color appears	Flavonoids present	(Katja, 2020)
Test for tannins	Extract + 2 mL $FeCl_3$	Blue and green colors appear	Tannins present	(Arrisujaya et al., 2019)
Test for alkaloids	Extract +HCl + Mayer reagent	White precipitate	Alkaloids present	(Endah, 2017)
Test for terpenoids	Extract + chloroform + H_2SO_4	Brownish color appears	Terpenoids present	(Bhernama, 2020)

In vitro sugar tolerance study

Sample preparation

The ethanol extract was dissolved in 50% DMSO to make a 100 mg/mL solution, which was then further diluted to concentrations of 50, 25, 12.5, and 6.25 mg/mL. These samples were evaluated for their α-glucosidase inhibition (AGI) and α-amylase inhibition (AAI) activities, with each sample being tested twice (Duplo). The AGI and AAI assay was carried out utilizing our previous protocol (Benedé-Ubieto et al., 2020; Puteri et al., 2020; Sornalakshmi et al., 2016).

Alpha-glucosidase inhibition

The AGI assay was conducted in 2 µL microtubes. 100 µL of sample solution was used for samples and sample blanks; for controls and control blanks, 100 µL of 50% DMSO was utilized. 600 µL of potassium phosphate buffer (0.1 M, pH 6.9) was added to the blanks. 200 µL of the substrate solution-56 mM sucrose in potassium phosphate buffer-was added to each tube. Rat intestinal glucosidase solution in 400 µL was added to the sample and control tubes. Tubes were mixed and then incubated for 55 min at 37°C. Following incubation, each tube received 750 µL of Tris-HCl solution (2M, pH 9). The liquids were run through a glass pipette containing a cotton column and one centimeter of aluminum oxide. The absorbance was then measured at 505 nm using a microplate reader to determine enzyme inhibition (Hendra et al., 2021).

The method utilized to assess the inhibition of sucrose hydrolysis was also applied to maltose hydrolysis, with a couple of modifications: maltose solution (3.5 mM) was substituted for the sucrose solution (56 mM), and the volume of enzyme solution was decreased from 0.4 mL to 0.2 mL.

Alpha-amylase inhibition

The AAI assay was conducted in a 1.5 mL sampling tube. The mixture for the reaction included 100 µL of sample and 350 µL of starch azure solution (4 mg/mL). After a 5-min pre-incubation, 50 µL of swine pancreatic α-amylase (0.5 unit/mL) was added, and the enzymatic reaction was then incubated at 37°C for 10 min in a water bath shaker. After stopping the process with a 50 µL solution of 50% acetic acid, the mixture was centrifuged for five minutes at 9000 rpm. A 96-well plate containing 200 µL of the supernatant was used for analysis, and the absorbance of the sample was measured at 595 nm (Hendra et al., 2021; Puteri et al., 2020).

The difference between the two absorbances was used to compute the AGI and AAI activity, which was then expressed as a percentage of inhibition, as presented in Equation 1. The results were expressed as the concentration at which the enzyme activity was reduced by 50% (IC_{50}), calculated using a statistical method called regression analysis.

$$\%\ Inhibition = \frac{(A_{control} - A_{control\ blank}) - (A_{sample} - A_{sample\ blank})}{(A_{control} - A_{control\ blank})} \quad \text{.....(1)}$$

A $_{sample}$ is the absorbance while EEF is present, whereas A $_{control}$ is the absorbance value for the control. Reaction blanks were prepared using sodium phosphate buffer rather than intestinal acetone powder (Hendra et al., 2021; Puteri et al., 2020).

In vivo study in normal mice

The investigation employed male Swiss mice, aged between 2 to 3 months and with a body weight of 20 to 30 g. They were allowed a two-week acclimatization period to the laboratory conditions. Ethical approval for this study was obtained from Gadjah Mada University, with the approval code KE/FK/0323/EC/2022.

Glucose tolerance test (GTT)

Prior to the trial, normal mice were subjected to an overnight fast and given unrestricted access to water. They were then orally given different treatments in five groups: 40 mg/kg Acarbose (positive control), 0.8, 1.67, and 3.3 g/kg EEF, and CMC-Na (negative control). After 30 minutes, the mice were administered 2 g/kg of oral glucose (Chaimum-am et al., 2017). Blood glucose levels (BGL) were measured using a glucometer at different intervals, as illustrated in Figure 1 (Fransisca et al., 2018; Benedé-Ubieto et al., 2020; Sato et al., 2023).

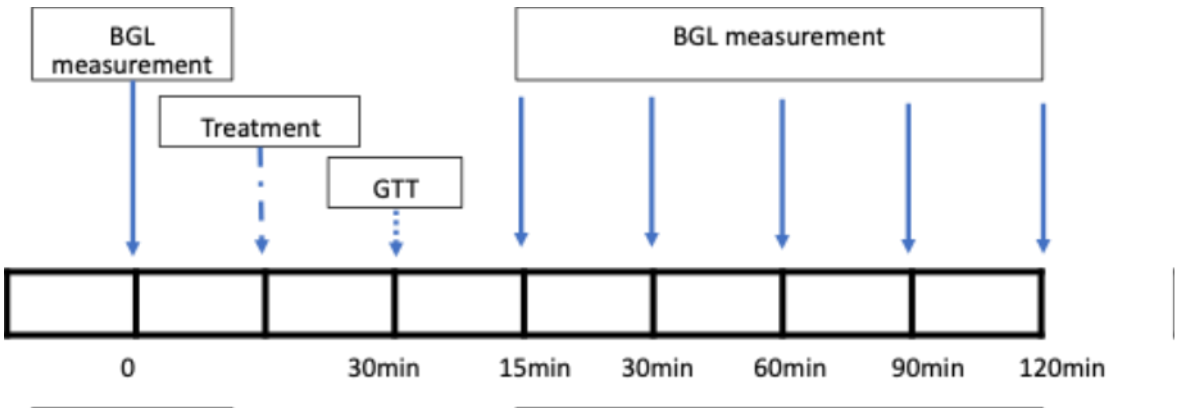

Figure 1. The timeline for the GTT

Note: BGL= blood glucose level; GTT = glucose test tolerance

Sucrose tolerance test

An identical protocol was used to determine glucose tolerance and conduct the sucrose tolerance test. However, sucrose was administered at 4 g/kg instead of glucose (Gunawan-Puteri et al., 2018; Luyen et al., 2018).

Starch tolerance test

The same method used to measure blood sugar levels after glucose injection was also used to measure blood sugar levels after starch intake, except that starch was given instead of glucose (Ogunyemi et al., 2022; Weng et al., 2021).

Data Analysis

We conducted data analysis using a one-way ANOVA, followed by a Bonferroni test, and considered a significant difference if the P-value < 0.05.

RESULT AND DISCUSSION

Phytochemical Screening

The Faloak leaves underwent phytochemical screening, identifying several secondary metabolites, as listed in Table 2. Analysis of an ethanol extract of Faloak leaves confirmed the presence of flavonoids, tannins, alkaloids, and terpenoids. Previous research has also documented the presence of these compounds in Faloak leaves (Dillak et al., 2019).

Table 2. Phytochemical constituents of ethanol extract from Faloak leaves

Metabolites	Results
Flavonoid	Positive
Tannins	Positive
Alkaloids	Positive
Terpenoids	Positive

Alpha-glucosidase inhibitors are a more valuable class of oral hypoglycemic treatments than other antidiabetic medications due to their effectiveness in treating postprandial hyperglycemia (Alssema et al., 2021). These inhibitors, like Acarbose, function by delaying the breakdown of carbohydrates, thereby prolonging the duration of the postprandial plasma glucose spike. This is crucial for preventing the absorption of carbs in the intestines and can be beneficial for treating diabetes mellitus and impaired glucose tolerance (Das et al., 2016). Consequently, an investigation was conducted to examine in vitro activity of α-glucosidase and α-amylase of the extract from Faloak leaves.

For the first time, the study shows that the ethanol extract from Faloak leaves significantly inhibits α-glucosidase and α-amylase in vitro. The IC_{50} values for the inhibition of maltose and sucrose were 65.36 and 30.37 mg/mL, respectively. Additionally, the IC_{50} for the inhibitory effect of α-amylase is 27.02 mg/mL. Based on the results, it is suggested that the ethanol extract of Faloak leaves may possess α-glucosidase inhibitory properties.

The impact of Faloak's ethanol extract on blood glucose levels was assessed using a sugar-loading test, as the inhibition of α-amylase and α-glucosidase can reduce postprandial glucose levels. The widely recognized oral sugar tolerance test was employed to screen hypoglycemic activity. Following the sugar challenge test, a significant increase in blood glucose levels was observed (Benedé-Ubieto et al., 2020). This phenomenon may be attributed to either a decrease in insulin secretion, an increase in hepatic glucose synthesis, or a reduction in tissue glucose utilization (Dilworth et al., 2021).

The graph in Figure 2 shows the blood glucose in normal mice at various time intervals (0–120 min) after they were orally given glucose, sucrose, and starch. The ethanol extract of Faloak considerably decreased the elevation of blood glucose following glucose loading, according to the findings of the glucose tolerance test (2 g/kg). All dosages of the Faloak ethanol extract significantly ($P<0.05$) lowered blood glucose levels in normal mice in a dose-dependent manner as compared to the glucose group (Table 3). The extract with the most significant percentage reduction in AUC (33.6%) was found at 3.3 g/kg. The mice that received glucose experienced a noticeable ($P<0.05$) reduction in their blood sugar levels when treated with Acarbose.

Normal mice administered sucrose showed that Acarbose and all the ethanol extract of Faloak reduced AUC significantly ($P<0.05$). The highest amount of blood glucose was lowered (36.6%) by the 3.3 g/kg ethanol extract of Faloak, which was followed by Acarbose, 1.67 g/kg of Faloak ethanol extract, and 0.8 g/kg (27.3, 25.0, and 20.9%) respectively. These data correlated with the ethanol extract from the Faloak dose.

The starch tolerance test findings demonstrated that Acarbose significantly decreased the AUC (34.6%) ($P<0.05$). Normal mice fed starch had considerably ($P<0.05$) lower blood sugar levels after being treated with ethanol extract from Faloak leaves. However, the ethanol extract of Faloak showed the greatest reduction in blood glucose at 3.3 g/kg, accounting for a 45.9% reduction. This was followed by 1.67 g/kg (42.3%) and 0.8 g/kg (33.6%).

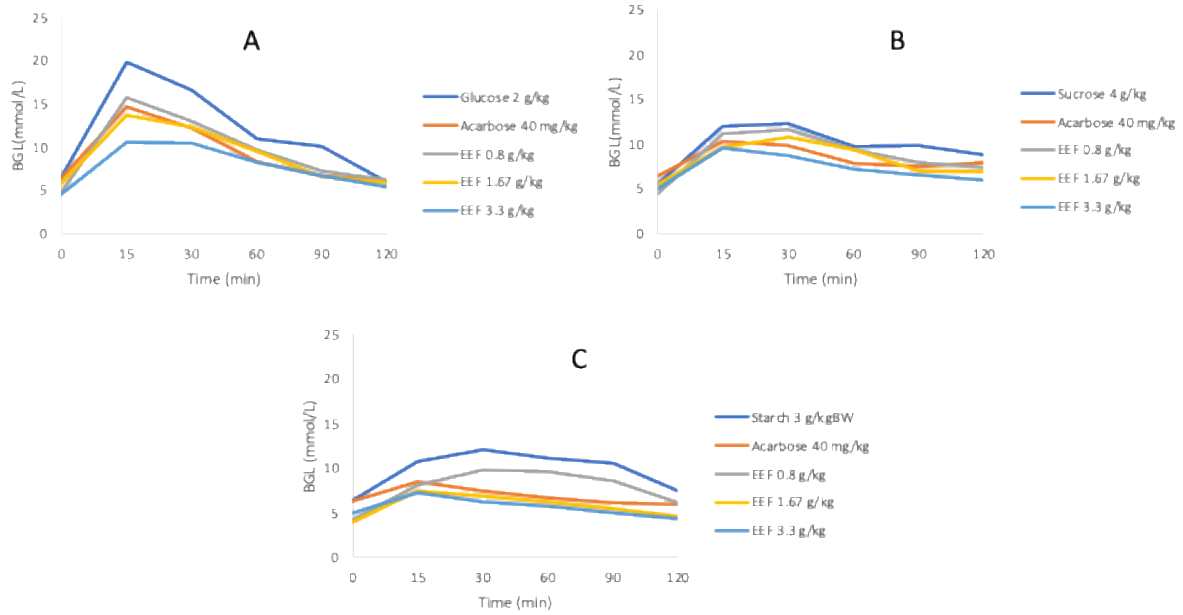

Figure 2. Effects of extract of Faloak on sugar tolerance test. A. Glucose tolerance test; B. Sucrose tolerance test; C. Starch tolerance test; EEF: ethanol extract of Faloak leaves

Table 3. Effect of extract of Faloak on sugar tolerance test in mice

Treatment	AUC (mg.min/dL)	% reduction AUC
Glucose 2 g/kg	1440.9 ± 43.2	-
Acarbose 40 mg/kg	1087.3 ± 48.8[a]	24.5
EEF 0.8 g/kg	1167.8 ± 73.2[a]	18.9
EEF 1.67 g/kg	1097.9 ± 60.4[a]	23.8
EEF 3.3 g/kg	956.2 ± 45.1[a]	33.6
Sucrose 4 g/kg	1384.8 ± 48.2	-
Acarbose 40 mg/kg	1006.2 ± 47.4[b]	27.3
EEF 0.8 g/kg	1094.9 ± 48.3[b]	20.9
EEF 1.67 g/kg	1024.8 ± 87.2[b]	25.9
EEF 3.3 g/kg	877.4 ± 50.4[b]	36.6
Starch 3 g/kg	1243.0 ± 30.3	-
Acarbose 40 mg/kg	813.1 ± 38.4[c]	34.6
EEF 0.8 g/kg	825.6 ± 26.9[c]	33.6
EEF 1.67 g/kg	717.0 ± 42.9[c]	42.3
EEF 3.3 g/kg	673.1 ± 46.8[c]	45.9

Note: All data is given as mean ±SD (n=5); [a] P<0,05 comparing treatment and glucose; [b] P<0,05 comparing treatment and sucrose (P<0,05); [c] P<0,05 comparing treatment and starch (P<0,05); EEF: ethanol extract of Faloak leaves; AUC: Area Under Curve

Our recent results revealed that the ethanol extract of Faloak could inhibit the alpha-glucosidase and alpha-amylase activity. Furthermore, after loading normal mice with glucose, sucrose, or starch, the ethanol extract of Faloak lowered the AUC and decreased the rise in blood glucose concentrations. The results demonstrated that after all sugar loading from the response for 120 min, the ethanol extract of Faloak at 3.3 g/kg had the greatest efficacy of lowering blood glucose when compared with Acarbose. The results align with previous studies by Julianus et al. (2023), indicating that a Faloak bark decoction reduces blood glucose by inhibiting alpha-glucosidase activity.

Several studies reported that flavonoids, tannins, and terpenoids are known to be bioactive antidiabetic principles. Their presence improves regulatory processes like insulin, possibly by enhancing peripheral glucose uptake or -cell glucose responsiveness. Their effectiveness may be further enhanced when they work together or separately (Darojati et al., 2022; Rahimi-Madiseh et al., 2016; Shamsudin et al., 2022; Sieniawska, 2015; Sornalakshmi et al., 2016). Ethanol as a solvent helps extract phytochemical components like flavonoids and tannins (Dias et al., 2021). Consequently, the effects of the Faloak leaf ethanol extract observed in this study might be attributed to their presence.

CONCLUSION

The present study elucidated the anti-hyperglycemic properties of the ethanolic extract of Faloak (*Sterculia quadrifida* R.Br.) leaves. Our findings demonstrate the extract's efficacy in lowering blood glucose levels through a dual mechanism: inhibiting key digestive enzymes (α-amylase and α-glucosidase) and reducing postprandial glucose levels. In vitro experiments revealed significant enzyme inhibition, while in vivo tests confirmed the extract's ability to mitigate glucose spikes. We have found several active ingredients that may be responsible for these pharmacological effects. However, more research is required to identify the specific compounds and understand their work. Our findings support the traditional uses of Faloak and provide scientific evidence for its potential in managing blood glucose levels. This comprehensive evaluation positions Faloak leaf extract as a promising candidate for developing natural anti-hyperglycemic interventions.

ACKNOWLEDGEMENT

The author acknowledges the funding for the research provided by Directorate of Academic Research and Community Service of Sanata Dharma University.

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