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Research Article

Antidiabetic Potential of *Arcangelisia flava* Merr. from Southeast Sulawesi: *In vitro* α -Glucosidase Inhibition and *in vivo* Evaluation

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Abstract

Background and Objective: The stem of *Arcangelisia flava* Merr., a medicinal plant from Southeast Sulawesi, has shown potential as a natural source of antidiabetic agents, but its activity requires further validation through *in vitro* and *in vivo* approaches. This study aimed to evaluate the antidiabetic activity of the stem extract and fractions of *A. flava* using *in vitro* and *in vivo* approaches. **Materials and Methods:** The *in vitro* assay was performed using a colorimetric α -glucosidase inhibition method with p-nitrophenyl-D-glucopyranoside (pNPG) as the substrate. The *in vivo* study was conducted using streptozotocin/nicotinamide-induced diabetic mice divided into 15 groups ($n=4$), including normal control, negative control, positive control, ethanol extract groups, n-hexane fraction groups, ethyl acetate fraction groups and butanol fraction groups. The extract was administered at doses of 250, 500 and 750 mg/kg bw, while each fraction was administered at doses of 28, 56 and 112 mg/kg bw. Data was analyzed using two-way repeated measures ANOVA. **Result:** The extract and fractions of *A. flava* stem exhibited α -glucosidase inhibitory activity and reduced fasting blood glucose levels in diabetic mice. Among the samples, the ethyl acetate fraction showed the strongest *in vitro* activity, with an IC_{50} value of 95.35 μ g/mL. *In vivo* evaluation also showed that the ethyl acetate fraction at 112 mg/kg bw produced the highest reduction in fasting blood glucose levels. The effects of the ethanol extract and ethyl acetate fractions at 56 and 112 mg/kg bw were comparable statistically ($p>0.05$) to glibenclamide. **Conclusion:** These findings suggest that Southeast Sulawesi yellow wood has promising antidiabetic potential and warrants further investigation for active compound identification and mechanism elucidation.

Key words: Antihyperglycemic effect, bioactive compounds, diabetic mice, enzyme inhibition, natural products

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Data Availability: All relevant data are within the paper and its supporting information files.

INTRODUCTION

Diabetes mellitus is a long-term metabolic disease marked by elevated blood glucose levels, which may occur due to insufficient insulin production, reduced insulin effectiveness, or a combination of both mechanisms. Over the past few decades, the number of people affected by diabetes has continued to rise, making it a significant public health concern at the global level. Data from the Global Burden of Disease Study estimated that around 529 million individuals worldwide were living with diabetes in 2021, with the figure expected to increase to more than 1.3 billion by 2050¹. A more recent pooled analysis of 1,108 population-representative studies involving 141 million participants found that nearly 828 million adults worldwide were living with diabetes in 2022. This figure highlights how rapidly the global diabetes burden has grown over the past three decades². Indonesia is among the countries with a high diabetes burden, reflecting the rapid epidemiological transition associated with urbanization, lifestyle changes, population ageing and increasing obesity². A national projection study estimated that diabetes prevalence in Indonesia would increase from 9.19% in 2020, corresponding to 18.69 million cases, to 16.09% in 2045, corresponding to 40.7 million cases. The same study further projected that the prevalence could be reduced to 15.68% with the implementation of prevention and control programs and to 9.22% if these programs were combined with risk factor prevention³. These findings emphasize the urgent need to strengthen diabetes prevention and treatment strategies in Indonesia, since the chronic hyperglycemia progressively damages multiple organ systems and drives severe complications. Although pharmacological therapy remains central to diabetes management, its long-term use may still be challenged by adverse effects, variable therapeutic responses, reinforcing the need for safer, effective, affordable⁴⁻⁶.

Natural products are still widely recognized as an important source for discovering and developing new drug candidates, especially because many plant-derived compounds can act on multiple biological targets involved in complex metabolic disorders such as diabetes⁷. *A. flava* Merr. is a medicinal plant from the Menispermaceae family that has been traditionally used in several Southeast Asian countries, including Indonesia, Malaysia and the Philippines⁸. The stem of *A. flava* Merr. has traditionally been used for the treatment of various disorders, including diarrhea, jaundice, malaria, fever, gastrointestinal disorders and inflammation-related conditions⁸. In West Sumatra Indonesia,

it is traditionally used for jaundice, digestive disorders, diarrhea⁹. Several studies have reported its activity against metabolic disorders, including antihyperuricemic^{10,11}, antihyperlipidemic¹², wound healing¹³, antioxidant and antidiabetic¹⁴. The antidiabetic activity of this plant is of particular interest. Previous studies have mainly focused on the leaves and roots of this species. Earlier *in vivo* studies reported that the root extract of *A. flava* was able to reduce blood glucose levels in experimental animals^{14,15}, while the leaf extract was found to inhibit α -glucosidase and amylase enzymes. However, the antidiabetic potential of the stem remains poorly explored, although this plant part contains various bioactive metabolites, such as berberine, palmatine, jatrorrhizine, flavonoids and phenolic compounds, which have been associated with glucose regulation, enzyme inhibition, antioxidant activity and pancreatic β -cell protection^{16,17}. Berberine has also been reported to inhibit α -glucosidase activity¹⁶. Nevertheless, studies investigating the antidiabetic activity of *A. flava* Merr. samples originating from Sulawesi remain very limited. Therefore, further investigation of the stem of Sulawesi-origin *A. flava* Merr. is needed to strengthen the scientific basis for developing this plant as a potential source of antidiabetic agents.

Findings from our previous study provide additional evidence supporting the stem of *A. flava* Merr. as a potential source of antidiabetic agents. In that study, the extract and its fractions reduced hyperglycemia in experimental animals based on the oral glucose tolerance test (OGTT). GC-MS analysis identified several bioactive compounds in the n-hexane fraction, including 7,4-hydroxy-3,5-bis(isopropyl)benzaldehyde, strychnine, 1-acetyl-20 α -hydroxy-16-methylene-. *In silico* network pharmacology analysis also suggested that these compounds may contribute to antidiabetic activity by inhibiting the AGE-RAGE signaling pathway, which plays an important role in the onset and progression of diabetic complications¹⁸. Further exploration was conducted in the present study by evaluating the antidiabetic activity through an *in vitro* α -glucosidase inhibition assay and an *in vivo* study using diabetes-induced animal models.

MATERIALS AND METHODS

Study area and duration: The experiment was conducted at the Pharmacology Laboratory Faculty of Pharmacy and the Animal Laboratory Faculty of Medicine Universitas Halu Oleo, Kendari city Southeast Sulawesi Province, Indonesia. This study was conducted from February to June 2026.

Materials: A glucometer set (Autocheck®, General Life Biotechnology Co., Ltd., New Taipei City, Taiwan), an ELISA reader (Thermo Scientific®, Thermo Fisher Scientific Inc., Waltham, MA, USA), acarbose (Dexa Medica®, Palembang, South Sumatra, Indonesia), acetic anhydride (Emsure® grade, Merck, Darmstadt, Germany), phosphate buffer pH 7 prepared in house, dimethyl sulfoxide (DMSO) (Sigma-Aldrich®, St. Louis, MO, USA), bovine serum albumin (BSA) (Sigma-Aldrich®, St. Louis, MO, USA), p-Nitrophenyl α -D-Glucopyranoside (pNPG) substrate (Sigma-Aldrich®, St. Louis, MO, USA), α -Glucosidase enzyme (Sigma-Aldrich® St. Louis, MO, USA), chloroform (Emsure®, Merck KGaA, Darmstadt, Germany), streptozotocin (Sigma-Aldrich®, St. Louis, MO, USA), citrate buffer pH 4.5 (Biogear®, supplied by PT Multi Indo Medika, Makassar, South Sulawesi, Indonesia), nicotinamide (Sigma-Aldrich®, St. Louis, MO, USA), 0.9% NaCl (Otsuka®, Indonesia, Lawang, Malang, East Java, Indonesia) and glibenclamide (First Medifarma®, Sidoarjo, East Java, Indonesia).

Sample preparation: Yellow wood stems were collected from Watumotobe Village, Kapontori District, Buton Regency, Southeast Sulawesi, Indonesia, located at approximately 5°14 17"S and 122°50 7"E (-5.23806, 122.83528). The sample was identified at the Research Laboratory of the Faculty of Pharmacy, Universitas Halu Oleo under registration number 150a/DST/UN29-21.2.2/PP 00.01/2026 and specimen number FF-UHO-178-020b. The stem samples (12.83 kg) were collected, washed, chopped and dried in an oven at 50°C, then reduced in size to obtain dried simplicia powder (4.2 kg). The simplicia powder (500 g) was macerated with 96% ethanol for 3 × 24 hours. The macerate was collected and concentrated using a rotary vacuum evaporator to obtain a crude ethanol extract. The ethanol extract (200 g) was fractionated using the trituration method with solvents of increasing polarity, namely n-hexane, ethyl acetate and butanol. The extract was placed in a mortar and pestle and n-hexane was added gradually while being gently ground. The filtrate was collected and concentrated to obtain a crude n-hexane fraction (7.3 g). Ethyl acetate was then added to the residue and gently ground; the filtrate was collected and evaporated to obtain a crude ethyl acetate fraction (28.7 g). The same procedure was carried out using butanol to obtain a crude butanol fraction (164 g). The extract and fractions were subsequently used for *in vitro* and *in vivo* antidiabetic assays.

Antidiabetic *in vitro* against α -glucosidase enzyme: The *in vitro* antidiabetic assay was performed according to our previous method with slight modifications¹⁹. The

α -glucosidase inhibition assay was performed using three independent biological replicates, with each replicate analyzed in triplicate as technical replicates. The results are presented as the Mean $\pm$ Standard Deviation. A 10 ppm acarbose stock solution was prepared by dissolving 1 mg of acarbose in 100 mL of phosphate buffer at pH 7.0. Meanwhile, the extract and fraction stock solutions were prepared by dissolving 10 mg of each sample in 10 mL of phosphate buffer at pH 7.0, resulting in a concentration of 1000 ppm. The stock solutions were then serially diluted to obtain working concentrations of 100, 200, 300, 400 and 500 ppm. The α -glucosidase inhibitory activity assay was performed using a 96-well microplate method. Each well was filled with 36 μ L of phosphate buffer at pH 7.0, followed by the addition of 30 μ L of acarbose standard solution at concentrations of 0.2-1.0 ppm or 30 μ L of sample solution at concentrations of 200-500 ppm. Subsequently, 17 μ L of 5 mM p-Nitrophenyl-D-Glucopyranoside (PNPG) substrate was added to each well and the mixture was incubated at 37°C for 5 minutes. After the initial incubation, 17 μ L of α -glucosidase enzyme solution was added and the reaction mixture was further incubated at 37°C for 15 minutes. The enzymatic reaction was stopped by adding 100 μ L of 200 mM Na₂CO₃ solution. The absorbance was then measured at 405 nm using an ELISA microplate reader²⁰. The percentage of α -glucosidase inhibition and the IC₅₀ value were calculated²¹. The IC₅₀ values were estimated by linear regression analysis of sample concentration versus percentage inhibition using Microsoft Excel®. Antidiabetic activity was classified as very strong (IC₅₀ < 50 μ g/mL), strong (50-100 μ g/mL), moderate (100-150 μ g/mL), weak (150-200 μ g/mL), or very weak (>200 μ g/mL)²².

Ethical statement: All animal procedures were performed according to applicable ethical regulations and the National Institutes of Health (NIH) Guide for the Care and Use of Laboratory Animals. This study received ethical approval from the Research Ethics Committee of Mandala Waluya University under approval number 080/KEP-UMW/VI/2026.

Antidiabetic *in vivo* assay: A total of 60 adult male BALB/c mice (*Mus musculus*) aged 2-3 months and weighing 20-30 g were obtained from the E-Mentik breeding facility in Kendari, Indonesia. Before the experiment, the mice were acclimatized for seven days under standard laboratory conditions. During this period, the mice were given standard feed and water, housed under a 12 hrs light/dark cycle²³. On the eighth day, the mice were fasted for 12 hrs before baseline fasting blood glucose levels were measured using a glucometer and

these values were recorded as Day 0 (D0). Experimental diabetes in rats was induced using the streptozotocin-nicotinamide (STZ-NA) model. The mice were first given nicotinamide intraperitoneally at 110 mg/kg body weight, followed 15 min later by streptozotocin administered intraperitoneally at 45 mg/kg body weight. Seven days after induction, fasting blood glucose levels were reassessed to confirm hyperglycemia. Mice with fasting blood glucose levels above 176 mg/dL were considered diabetic and subsequently included in the treatment phase^{24,25}. Diabetic mice were randomly assigned to twelve experimental groups, with four animals in each group. The study groups consisted of a normal control group (KN) administered 0.5% sodium carboxymethyl cellulose (Na-CMC), a negative control group (K⁻) receiving 0.5% Na-CMC and a positive control group (K⁺) treated with glibenclamide at a dose of 0.013 mg/20 g body weight. Treatment groups KP1-KP3 received ethanol extract at 125, 250 and 500 mg/kg bw, respectively; KP4-KP6 received n-hexane fraction at 28, 56 and 112 mg/kg bw, respectively; KP7-KP9 received ethyl acetate fraction at 28, 56 and 112 mg/kg bw, respectively; KP10-KP12 received butanol fraction at 28, 56 and 112 mg/kg bw. The sample size for each treatment group was determined using Federer's formula²⁶. The minimum sample size calculated using Federer's formula was three animals per treatment group. However, this study used four animals in each of the 12 treatment groups. All treatments (extract, fractions and control) were administered orally once daily according to the assigned group²⁷. Fasting blood glucose levels after treatment were measured on Days 7 (D7) and 14 (D14) following treatment initiation. The percentage reduction in blood glucose levels was calculated²⁸.

Analysis data: Data are expressed as Mean $\pm$ Standard Deviation (SD). Fasting blood glucose levels were statistically analyzed using IBM SPSS Statistics version 30. Data normality and homogeneity were assessed before analysis. Data normality was assessed using the Shapiro-Wilk test and homogeneity of variance was evaluated using Levene's test of equality of error variances. A p-value greater than 0.05 was considered to indicate normally distributed data and homogeneous variances. No missing data or influential outliers were identified. All observations were included in the analysis. Statistical analysis was performed using two-way repeated-measures ANOVA, followed by LSD post hoc testing. Differences between groups were considered statistically significant at $p < 0.05$. Data were visualized using GraphPad Prism 11 software (GraphPad Software Inc., San Diego, CA, USA).

RESULTS AND DISCUSSION

Arcangelisia flava Merr. inhibits the α -glucosidase enzyme: The α -glucosidase inhibitory activity of the ethanol extract and fractions of *A. flava* Merr. is presented in Table 1. All samples exhibited inhibitory activity against α -glucosidase, with varying levels of potency among the extract and fractions. Among the samples, the ethyl acetate fraction showed the most potent inhibitory activity, as reflected by the lowest IC₅₀ value. The inhibitory activity of this fraction was stronger than that of the butanol and *n*-hexane fractions, while the ethanol extract displayed the weakest activity. These results indicate that fractionation improved the α -glucosidase inhibitory activity of *A. flava* Merr., particularly in the ethyl acetate fraction. The pronounced activity of the ethyl acetate fraction suggests that the compounds responsible for α -glucosidase inhibition are likely enriched in the semi-polar fraction. This is consistent with previous reports showing that fractionation of crude plant extracts can concentrate bioactive constituents into specific solvent fractions, thereby improving their enzyme inhibitory potency²⁹. In contrast, the lower activity of the ethanol extract may be associated with its more complex chemical composition, in which inactive or less active constituents may reduce the relative contribution of the active compounds. Although the ethyl acetate fraction was the most active sample among the extract and fractions, its inhibitory potency was lower than that of acarbose as the positive control. Nevertheless, these findings indicate that the ethyl acetate fraction of *A. flava* Merr. has potential for further development as a natural source of α -glucosidase inhibitors.

Antidiabetic activity of *Arcangelisia flava* Merr. *in vivo*:

Diabetes was induced in experimental animals by intraperitoneal administration of streptozotocin/nicotinamide. Animals were considered diabetic when their fasting blood glucose levels exceeded 176 mg/dL. The *in vivo* antidiabetic activity of *A. flava* Merr. extract and its fractions were evaluated based on changes in blood glucose levels measured on D0, D7 and D14, as well as the percentage reduction in blood glucose levels after treatment. The results showed that blood glucose profiles differed significantly across the observation periods D0, D7 and D14 ($p < 0.05$). As presented in Table 2, the normal control group maintained stable blood glucose levels throughout the study, with no significant differences among D0, D7 and D14, confirming that normal glucose homeostasis was preserved during the observation period. In contrast, the negative control group (K⁻) showed significant differences among all observation times ($p < 0.05$),

Table 1: IC₅₀ values of *Arcangelisia flava* Merr. samples against the α-glucosidase enzyme

Sample	IC ₅₀ α-Glucosidase
Acarbose	0.370±0.01
Extract ethanol	176.01±0.95
Fraction n-Hexane	157.94±0.54
Fraction ethyl acetate	95.35±0.52
Fraction butanol	148.83±0.32

Data are presented as mean ±SD from three replicates (n = 3)

Table 2: Effect of *A. flava* Merr. extract and fractions on blood glucose levels in diabetic mice

Groups	Blood glucose level (mg/dL) ±SD		
	D0	D7	D14
KN	89.00±2.58	89.75±3.59 ^{bc}	88.25±3.20 ^{bc}
K ⁻	177.50±1.29 ^a	236.50±1.73 ^{ac}	266.00±4.24 ^{ac}
K ⁺	403.00±5.89 ^a	142.00±3.56 ^{ab}	115.00±4.24 ^{ab}
KP1	199.75±5.89 ^a	120.00±2.94 ^{abc}	108.75±8.54 ^{ab}
KP2	235.50±3.87 ^a	138.75±5.91 ^{ab}	107.50±7.72 ^{ab}
KP3	235.50±3.42 ^a	123.75±6.50 ^{abc}	99.50±4.51 ^{abc}
KP4	188.75±3.10 ^a	132.00±5.89 ^{abc}	129.25±4.50 ^{abc}
KP5	205.00±4.40 ^a	130.00±6.38 ^{abc}	126.25±3.30 ^{abc}
KP6	254.00±4.16 ^a	136.25±3.69 ^{ab}	125.00±4.24 ^{abc}
KP7	192.25±5.19 ^a	122.25±6.02 ^{abc}	102.00±5.77 ^{abc}
KP8	278.25±4.19 ^a	143.00±5.72 ^{ab}	117.25±1.89 ^{ab}
KP9	346.25±5.91 ^a	148.50±4.93 ^{ab}	116.00±4.55 ^{ab}
KP10	227.00±2.16 ^a	149.25±7.93 ^{ab}	127.00±7.07 ^{abc}
KP11	196.25±4.86 ^a	131.00±7.79 ^{abc}	101.25±5.32 ^{abc}
KP12	215.50±4.36 ^a	123.75±5.19 ^{abc}	103.25±7.54 ^{abc}

Data is presented as Mean ±SD from four replicates (n = 4) each group. Statistical analysis is indicated as follows: (a) significant difference (p<0.05) compared to the normal control group (KN); (b) significant difference (p<0.05) compared to the negative control group (K⁻); and (c) significant difference (p<0.05) compared to the positive control group (K⁺). The normal control group (KN) (normal, 0.5% Na-CMC), negative control group (K⁻) (diabetic, 0.5% Na-CMC), positive control group (K⁺) (diabetic, glibenclamide 0.013 mg/20 g bw). Treatment groups KP1-KP3 (diabetic, ethanol extract at 125, 250 and 500 mg/kg bw, respectively); KP4-KP6 (diabetic, n-hexane fraction at 28, 56 and 112 mg/kg bw, respectively); KP7-KP9 (diabetic, ethyl acetate fraction at 28, 56 and 112 mg/kg bw, respectively); KP10-KP12 (diabetic, received butanol fraction at 28, 56 and 112 mg/kg bw

with a progressive increase in blood glucose levels. This finding indicates that the streptozotocin/nicotinamide-induced diabetic model successfully elevated fasting blood glucose levels. The persistent increase in blood glucose levels until D14 further confirms that hyperglycemia continued to worsen in untreated diabetic mice.

The extract and fractions of *A. flava* Merr. exhibited anti-hyperglycemic activity in diabetic mice, as indicated by a reduction in fasting blood glucose levels during the treatment period. The decrease in blood glucose levels was observed from D7 and continued until D14 in all treatment groups. Based on the percentage reduction at D14, the ethyl acetate fraction at 112 mg/kg bw showed the highest glucose-lowering effect, followed by the ethyl acetate fraction at 56 mg/kg bw, extract at 500 mg/kg bw, extract at 250 mg/kg bw, butanol fraction at 112 mg/kg bw and n-hexane fraction at 112 mg/kg bw, with reductions of 66.50, 57.86, 57.75, 54.35, 52.09 and 50.79%, respectively (Table 3). Further statistical analysis was performed to compare blood glucose levels among treatment groups at each observation

time. The results showed that all groups treated with *A. flava* extract and fractions had significantly lower blood glucose levels than the negative control group (K⁻) at D7 and D14 (p<0.05), indicating that the tested samples effectively reduced fasting blood glucose levels in diabetic mice. The glucose-lowering effectiveness of the samples was further evaluated by comparison with the positive control group (K⁺), which received glibenclamide. At D7, the extract at 250 mg/kg bw, n-hexane fraction at 112 mg/kg bw, ethyl acetate fractions at 56 and 112 mg/kg bw and butanol fraction at 28 mg/kg bw showed blood glucose levels comparable to those of K⁺ (p>0.05) (Table 2). At D14, only the extract at 125 and 250 mg/kg bw and the ethyl acetate fractions at 56 and 112 mg/kg bw remained statistically comparable to K⁺ (p>0.05), whereas the n-hexane and butanol fractions differed significantly from K⁺ (p<0.05). The statistical analysis between treatment groups also showed that the ethyl acetate fraction at 56 mg/kg bw was not significantly different from the 112 mg/kg bw dose (p>0.05) and the groups treated with ethanol extract also showed fasting blood glucose-lowering

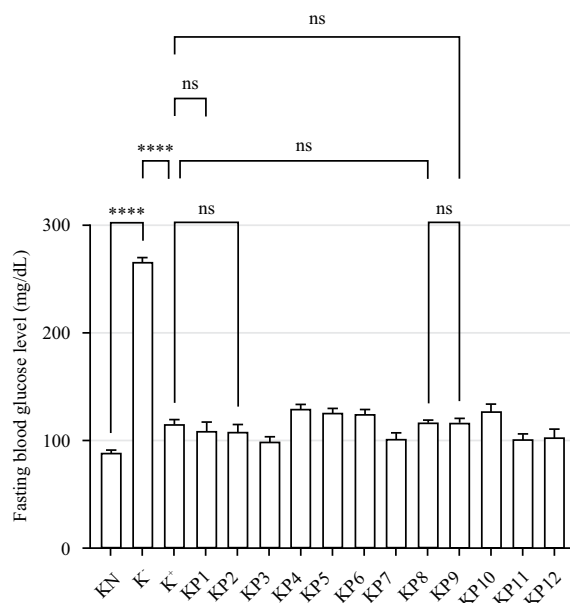


Fig. 1: Statistical comparison of fasting blood glucose levels in diabetic mice at D14 after treatment with *A. flava* Merr. extract and fractions

Data are presented as Mean $\pm$ SD, ****indicates a significant difference ($p < 0.05$), while ns indicates no significant difference. The normal control group (KN) (normal, 0.5% Na-CMC), negative control group (K-) (diabetic, 0.5% Na-CMC), positive control group (K+) (diabetic, glibenclamide 0.013 mg/20 g bw). Treatment groups KP1-KP3 (diabetic, ethanol extract at 125, 250 and 500 mg/kg bw, respectively); KP4-KP6 (diabetic, n-hexane fraction at 28, 56 and 112 mg/kg bw, respectively); KP7-KP9 (diabetic, ethyl acetate fraction at 28, 56 and 112 mg/kg bw, respectively); KP10-KP12 (diabetic, received butanol fraction at 28, 56 and 112 mg/kg bw)

Table 3: Percentage reduction in blood glucose levels following treatment with *A. flava* Merr. extract and fractions in diabetic mice

Groups	Percentage decrease in blood glucose levels	
	D7	D14
KN	-0.84 $\pm$ 3.000	0.84 $\pm$ 1.93
K-	-33.24 $\pm$ 1.57	-49.86 $\pm$ 2.44
K+	64.76 $\pm$ 1.39	71.46 $\pm$ 0.96
KP1	39.92 $\pm$ 1.72	45.56 $\pm$ 4.45
KP2	41.08 $\pm$ 2.90	54.35 $\pm$ 3.94
KP3	47.45 $\pm$ 3.21	57.75 $\pm$ 2.19
KP4	30.07 $\pm$ 3.65	31.52 $\pm$ 3.03
KP5	36.59 $\pm$ 2.41	38.41 $\pm$ 1.30
KP6	46.36 $\pm$ 1.31	50.79 $\pm$ 1.30
KP7	36.41 $\pm$ 3.79	46.94 $\pm$ 1.77
KP8	48.61 $\pm$ 1.70	57.86 $\pm$ 0.91
KP9	57.11 $\pm$ 2.15	66.50 $\pm$ 1.58
KP10	34.25 $\pm$ 3.28	44.05 $\pm$ 2.97
KP11	33.25 $\pm$ 3.51	48.41 $\pm$ 1.46
KP12	42.58 $\pm$ 2.27	52.09 $\pm$ 2.83

Data is presented as mean $\pm$ SD from four replicates ($n = 4$) each group. The normal control group (KN) (normal, 0.5% Na-CMC), negative control group (K-) (diabetic, 0.5% Na-CMC), positive control group (K+) (diabetic, glibenclamide 0.013 mg/20 g bw). Treatment groups KP1-KP3 (diabetic, ethanol extract at 125, 250 and 500 mg/kg bw, respectively); KP4-KP6 (diabetic, n-hexane fraction at 28, 56 and 112 mg/kg bw, respectively); KP7-KP9 (diabetic, ethyl acetate fraction at 28, 56 and 112 mg/kg bw, respectively); KP10-KP12 (diabetic, received butanol fraction at 28, 56 and 112 mg/kg bw)

effects that were not significantly different from those observed in the ethyl acetate fraction-treated groups (Fig. 1 and Table 2). This finding suggests that increasing the dose from 56 to 112 mg/kg bw did not produce a statistically greater glucose-lowering effect in D14. The antihyperglycemic

response of the ethyl acetate fraction may have reached an effective range at 56 mg/kg bw. In addition, the ethanol extract-treated groups showed fasting blood glucose-lowering effects that were not significantly different from those of the ethyl acetate fraction-treated groups. This

may indicate that the crude ethanol extract already contains bioactive compounds responsible for the antidiabetic activity, while fractionation into ethyl acetate may enrich these active constituents and maintain or enhance their therapeutic potential.

The development of diabetes mellitus therapy has increasingly shifted from single-target approaches toward agents capable of modulating multiple pathways involved in hyperglycemia and its complications³⁰. Although conventional antidiabetic drugs remain essential in clinical practice, their long-term use may be constrained by adverse effects, variable therapeutic responses, cost and limited accessibility. Consequently, natural products continue to attract considerable attention as promising sources of new antidiabetic candidates. Owing to their structural diversity and broad biological activities, plant-derived compounds are valuable resources in drug discovery, particularly for complex metabolic disorders such as diabetes^{7,31}. In diabetes research, medicinal plants are especially relevant because their bioactive compounds may work through several complementary mechanisms. In diabetes research, medicinal plants are especially relevant because their bioactive compounds may work through several complementary mechanisms. Accordingly, this study investigated the antidiabetic activity of Southeast Sulawesi yellow wood *A. flava* Merr. by integrating an *in vitro* α -glucosidase inhibition assay with an *in vivo* evaluation in experimentally induced diabetic animal models.

The *in vitro* α -glucosidase inhibition assay showed results that are consistent with previous reports on the antidiabetic potential of plant-derived compounds and *A. flava* Merr. Earlier studies demonstrated that yellow wood extracts from the leaves, stems and roots were able to inhibit α -glucosidase activity, with the aqueous stem extract showing a lower IC₅₀ value than the leaf extract³². These findings support the α -glucosidase inhibitory activity of the stem of *A. flava* Merr. However, enzymatic inhibition alone does not fully reflect the complex regulation of blood glucose under physiological conditions. Therefore, *in vivo* assessment was conducted to determine whether the extract and fractions could produce a glucose-lowering effect in diabetic mice. The results of this study indicate that the extract and ethyl acetate fraction were able to reduce blood glucose levels in a dose-dependent manner. The results of this study are also consistent with previous studies on the stem extract of *A. flava*, which demonstrated its ability to lower blood glucose levels in diabetic experimental animals, thereby further supporting its antidiabetic potential¹⁵. In line with this, our previous study using the Oral Glucose Tolerance Test (OGTT) also showed that

the extract and fractions of the stem of *A. flava* Merr. showed that the ethanol extract and ethyl acetate fraction exhibited glucose-lowering activity, with the ethanol extract at 500 mg/kg bw producing the highest percentage reduction in blood glucose levels, namely 50.25%, followed by glibenclamide at 43.53% and the ethyl acetate fraction at 125 mg/kg bw at 42.82%¹⁸. The stronger activity observed in the ethyl acetate fraction may be related to the enrichment of semi-polar bioactive compounds in this fraction. Some studies find that fractionation can enhance pharmacological activity by separating and concentrating bioactive constituents according to their polarity, allowing active compounds that are initially distributed in the crude extract to become enriched in specific fractions^{33,34}.

The comparable glucose-lowering effects observed between the samples in this study, suggest that the antidiabetic activity of *A. flava* Merr. may be associated with the presence and enrichment of active secondary metabolites. These effects may be attributed to the bioactive constituents present in this plant, as *A. flava* Merr. has been reported to contain isoquinoline alkaloids, flavonoids and phenolic compounds, which are commonly associated with antidiabetic activity^{16,35,36}. Among these compounds, berberine is one of the most important alkaloids that could regulate the glucose level *in vivo* experimental. Berberine has been identified in the stem³⁷ and ethyl acetate fraction³⁸ of *A. flava* Merr. The presence of this compound in the stem of *A. flava* may be one of the factors contributing to the reduction in blood glucose levels observed in the *in vivo* study. Previous studies on the antidiabetic activity of berberine have reported that this compound can improve glucose metabolism, enhance insulin sensitivity, reduce insulin resistance and activate AMP-Activated Protein Kinase (AMPK), a key regulator of cellular energy homeostasis¹⁶. It has also been reported to inhibit α -glucosidase activity, which may delay intestinal glucose absorption and contribute to the reduction of blood glucose levels^{16,39}. Another study about *A. flava* Merr. was found that the flavonoid fraction of yellow stem showed antihyperglycemic activity accompanied by modulation of oxidative stress-related enzymes¹².

CONCLUSION

Arcangelisia flava Merr. demonstrated antidiabetic potential through α -glucosidase inhibition and the reduction of fasting blood glucose levels in streptozotocin/nicotinamide-induced diabetic mice. The ethyl acetate fraction exhibited the strongest α -glucosidase inhibitory activity and produced a glucose-lowering effect comparable to glibenclamide. The

absence of a significant difference between the 56 and 112 mg/kg bw doses suggests that an effective antihyperglycemic response may already be achieved at the lower dose. However, this study was limited to preclinical models and the specific active compounds and underlying molecular mechanisms were not directly identified. Further studies are required to identify the bioactive compounds responsible for this activity and to elucidate their molecular mechanisms, particularly their effects on insulin secretion, insulin receptor signaling and GLUT4 expression and translocation.

SIGNIFICANCE STATEMENT

This study reveals that the stem of *A. flava* Merr. from Southeast Sulawesi possesses promising antidiabetic activity through α -glucosidase inhibition and reduction of fasting blood glucose levels in diabetic mice. The ethyl acetate fraction showed the most potent activity, supporting its potential as a natural source for the development of plant-derived antidiabetic agents. These findings provide a scientific basis for the traditional use of yellow wood and may serve as a reference for further development of medicinal plants as alternative sources of antidiabetic therapy.

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