

Antidiabetic Activity of *Arcangelisia flava* Stem Bark from Southeast Sulawesi Indonesia *In Vivo* Integrated with Network Pharmacology Analysis

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Abstract

The antidiabetic activity of *Arcangelisia flava* stem bark has not been previously reported. This study evaluated the antidiabetic and antioxidant activities of its extract and fractions, identified bioactive compounds, and explored potential mechanisms using network pharmacology. Chemical constituents of the n-hexane fraction were analyzed by gas chromatography-mass spectrometry (GC-MS). *In vivo* antidiabetic activity was assessed in streptozotocin/niacinamide-induced *Mus musculus* using the oral glucose tolerance test (OGTT), while antioxidant activity was determined by the ABTS assay. GC-MS identified 18 compounds classified into aromatic hydrocarbons, ketones and alcohols, phenolic aldehydes, sulfur compounds, terpenes, fatty acid derivatives, and alkaloids. The greatest reductions in blood glucose levels were observed in groups treated with ethanolic extract (500 mg/kgBW), glibenclamide, and ethyl acetate fraction (125 mg/kgBW), with reductions of 50.25%, 43.53%, and 42.82%, respectively. ABTS analysis showed IC₅₀ values of 8.00, 49.80, 110.25, 10.20, and 18.44 µg/mL for vitamin C, ethanolic extract, n-hexane fraction, ethyl acetate fraction, and butanol fraction, respectively. Network pharmacology analysis indicated that compounds 7 and 17 from the n-hexane fraction may exert antidiabetic effects through inhibition of the AGE-RAGE signaling pathway associated with diabetic complications. Key target proteins included MAPK1, MMP2, MAPK14, MAPK3, PIK3CA, and TGFBR1. Overall, *Arcangelisia flava* extracts and fractions demonstrate promising antidiabetic and antioxidant potential, although further *in vitro* and mechanistic studies are required to validate these findings.

Keywords: Antioxidant, AGE-RAGE, *Mus musculus*, Streptozotocin-nicotinamide, GC-MS

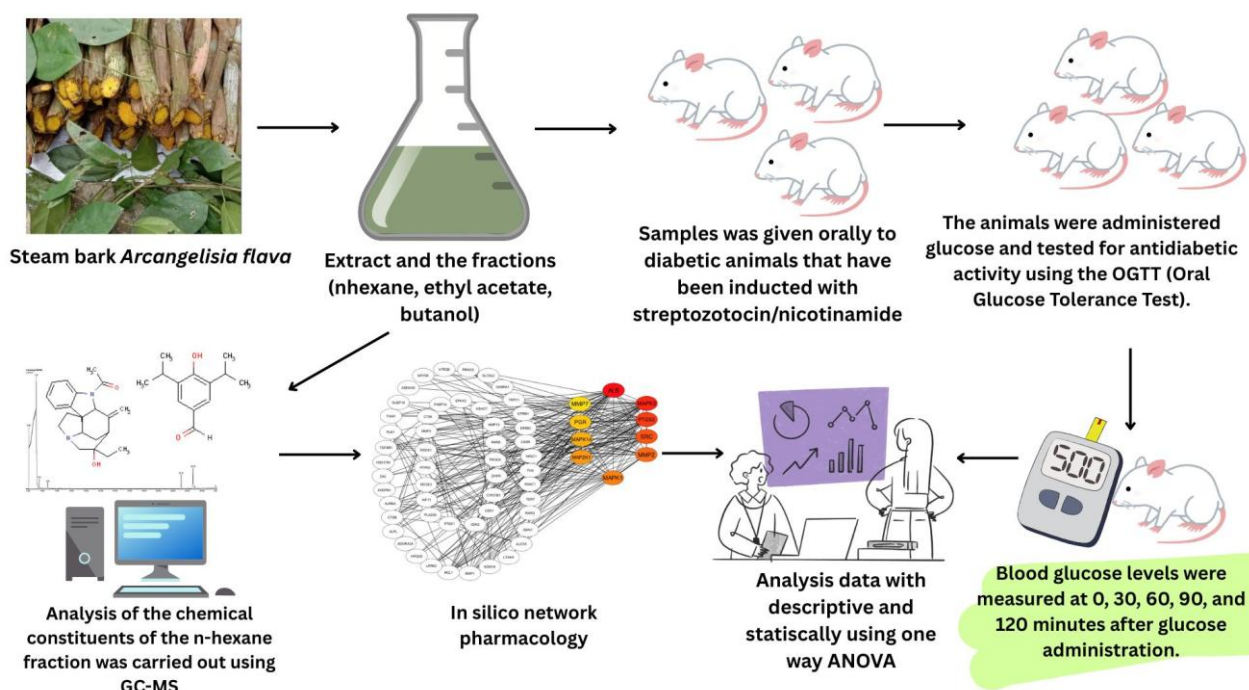
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Graphical Abstract



Introduction

Indonesia remains one of the countries with the greatest biodiversity in the world. In 2017, it was recorded that Indonesia possessed approximately 31,750 plant species, around 15,000 species were identified having potential medicinal properties. Unfortunately, only about 7,000 species have been utilized as raw materials for traditional or modern medicines [1]. Despite this, the use of plants in traditional medicine has long been an integral part of Indonesian culture. Historical evidence shows that Indonesians have practiced natural healing for generations, and traditional medicine continues to be a preferred choice for maintaining health and treating various diseases [2]. Originally based on empirical knowledge, this practice has drawn the attention of many researchers seeking to scientifically validate its pharmacological effects and develop it as a potential source of medicinal compounds. One plant that has recently gained research interest is *Arcangelisia flava*, which has been traditionally used across Southeast Asia to

treat various ailments, including infections, inflammation, and metabolic disorders[3]. In Kalimantan, local communities use it as an antiviral agent and as a remedy for jaundice, malaria, and cancer [4]. In other regions, decoctions made from the stem and root of *Arcangelisia flava* are traditionally used as a febrifuge, tonic, abortifacient, and treatment for hepatitis, indigestion, and malaria [5]. These long-standing empirical uses have encouraged researchers to further explore and scientifically substantiate the pharmacological potential of this plant.

Recent studies on *Arcangelisia flava* have revealed a wide range of pharmacological effects, making this plant a promising candidate for drug development. Several reports have demonstrated its activity against metabolic disorders, including antihyperuricemic [6, 7], antihyperlipidemic [8], wound healing [9], antioxidant, and antidiabetic [10]. Its pharmacological activity as an antidiabetic agent is particularly interesting, as diabetes mellitus remains one of the most prevalent metabolic diseases in Indonesia [11]. Therefore, the discovery and

development of antidiabetic agents whether as health supplements or as pharmaceutical raw materials are importance. However, studies investigating the antidiabetic potential of this plant remain limited. The root extract of *Arcangelisia flava* has been reported to reduce blood glucose levels in experimental animals [12], while the leaf extract was found to inhibit α -glucosidase and amylase enzymes [10]. There have been no reports on the antidiabetic activity of the stem bark of *Arcangelisia flava*. Interestingly, the stem bark is known to contain the alkaloid berberine, which has been reported to inhibit α -glucosidase activity, and in silico studies have shown its potential interaction with dipeptidyl peptidase-IV (DPP-IV), an enzyme that plays a critical role in the pathophysiology of diabetes mellitus. [13]. In addition, the antioxidant activity of *Arcangelisia flava* stem bark is also believed to contribute to its antidiabetic effect [14]. The use of antioxidants has long been associated with the prevention of diabetes mellitus through several mechanisms [15]. Nevertheless, the precise mechanisms underlying the antidiabetic effects of *Arcangelisia flava* remain to be fully elucidated.

Exploration of the antidiabetic mechanism of *Arcangelisia flava* requires further analysis using complementary methods to strengthen the existing findings. The in silico network pharmacology approach serves as a powerful tool to predict the mechanisms of drug compounds against pharmacological conditions through complex interactions involving multiple components and multiple targets [16]. Therefore, this study was conducted to evaluate the antidiabetic activity of *Arcangelisia flava* extract and fractions, identify their bioactive compounds, and investigate the mechanistic pathways of these compounds using the network pharmacology approach

Materials and Methods

Materials

Mice (*Mus musculus*) were obtained from the experimental mouse breeding facility E Mentik Kendari, glucose strips (Autocheck®), ethanol 96%, butanol (technical grade), ethyl acetate (technical grade), *n*-hexane (technical grade), concentrated HCl (technical grade), sodium carboxymethyl cellulose (Na CMC), streptozotocin (Sigma Aldrich®), nicotinamide (Sigma Aldrich®), glibenclamide (First Medifarma®), glucose (Merck®), (2,2-Azinobis(3-ethylbenzothiazoline)-6-sulfonic acid) ABTS (Sigma®), potassium persulfate (Nitra Kimia®), vitamin C (Sigma Aldrich®), and ammonium acetate buffer (Merck®). A set of equipment including a glucometer (Autocheck®), rotary vacuum evaporator (Buchi®), oven (Stuart®), water bath (B-ONC®), oral gavage (Govage®), and pH meter.

Extraction and Fractionation

Stem bark of *kayu kuning* stems (*Arcangelisia flava* (L.) Merr.) or Akar kuning plant [4], were collected from Kapontori District, Buton Regency, Southeast Sulawesi Province (-5.144479, 122.787238). The *Arcangelisia flava* stem were identified by Laboratory of the Department of Biology, Faculty of Mathematics and Natural Sciences, Halu Oleo University. The stem bark were processed by washing, cutting, drying at 50°C, and grounding into a fine simplicia powder. The simplicia powder (500 g) was macerated with 96% ethanol, the filtrate was concentrated using a rotary evaporator until a crude ethanolic extract was obtained. The extract (200 g) was subsequently fractionated using the trituration method with a gradient polarity solvent system. The extract was placed in a mortar, and *n*-hexane was gradually added while grinding until the

solvent became colorless. The filtrate was collected and concentrated using a rotary evaporator to obtain the *n*-hexane fraction. The remaining residue was then triturated successively with ethyl acetate and butanol. The ethyl acetate and butanol filtrates were collected and concentrated to obtain the concentrated ethyl acetate and butanol fractions. Extract, and the fractions were used for further analysis [17].

Identification of Chemical Compound using GC-MS/MS

The *n*-hexane fraction of *Arcangelisia flava* was subjected to GC-MS/MS analysis to identify its volatile constituents. The *n*-hexane fraction (1 g) was dissolved with distilled water (2 mL), homogenized for 10 min. Then, the ethyl acetate (10 mL) and anhydrous sodium sulfate (10 g) (Merck®, Germany) were added to remove residual moisture. The mixture was then sonicated for 10 minutes, and the sample was filtered through Whatman filter. The filtrate was evaporated with ultrasonic conditions to remove the ethyl acetate, and the crude residue was obtained. The residue was re-dissolved with *n*-hexane (1 mL) (Merck®, Germany), and put into tightly sealed GC vial. GC-MS/MS analysis was carried out using an Agilent 8890 gas chromatograph coupled with a Xevo® TQ-GC mass spectrometer (UK). Separation was achieved using a DB-5MS column (30 m × 250 µm × 0.25 µm), with helium as the carrier gas at a constant flow rate of 1.0 mL/min. The oven temperature program was set as follows: 110°C (held for 3.5 min), ramped at 10°C/min to 200°C (held for 1 min), then increased at 5°C/min to 280°C and maintained for 12 min, yielding a total runtime of 41.5 min. The injector operated in splitless mode at 280°C, with a 1 µL sample injection volume. The mass spectrometer was operated in electron ionization mode (EI+), scanning in the range of 50–500 *m/z*, with the ion source

temperature set at 200°C and the transfer line at 250°C. Compound identification was achieved by comparing the acquired spectra with the NIST library (version 2011) [18]. No authentic reference standards were used, and retention indices were not determined.

Preparation of Streptozotocin-Nicotinamide-Induced Diabetes Mellitus Solution

Nicotinamide was dissolved in sodium chloride solution 0.9% and administered intraperitoneally (i.p.) 15 min prior to the administration of streptozotocin at a dose of 110 mg/kgBW. Streptozotocin was dissolved in 50 mM citrate buffer (pH 4.5), stored in a glass bottle, and wrapped in aluminum foil to protect it from light. The streptozotocin solution was administered immediately after homogenization (within 5 min) at a dose of 45 mg/kg body weight via intraperitoneal injection [19].

In Vivo Antihyperglycemic Assay

The experimental animals used were male white mice (*Mus musculus*), aged 2–3 months and weighing 20–30 g. The ethical clearance for the use of experimental animals was issued by the Research and Community Service Institute of Halu Oleo University under approval number 182/UN29.20.1.2/PG/2025. The animals were acclimatized for seven days under controlled conditions (12-h light and 12-h dark cycles) and provided with a standard diet [20]. The initial blood glucose levels of the animals were measured prior to streptozotocin-nicotinamide induction. Each mouse was then injected intraperitoneally with nicotinamide solution (110 mg/kg body weight), followed 15 min later by an intraperitoneal injection of streptozotocin solution (45 mg/kg body weight). The animals were left for 72–120 h after induction, and their blood glucose levels

were measured on the third day post-induction as the blood glucose level to [21,22]. Animals with blood glucose levels greater than 176 mg/dL were considered hyperglycemic and subsequently divided into groups according to the experimental design [23].

The diabetic animals were divided into nine groups, with four mice in each group ($n = 4$). The normal control group (KN) (normal mice that received 0.5% Na-CMC), the negative control group (K-) (diabetic mice + 0.5% Na-CMC), the positive control group (K+) (diabetic mice + glibenclamide at a dose of 0.013 mg/20 gBW), the treatment groups were divided based on the type and dose of extract administered. Dose group 1 (KD1), dose group 2 (KD2), and dose group 3 (KD3) received the ethanolic extract at doses of 125 mg/kg, 250 mg/kg, and 500 mg/kg body weight, respectively. Dose group 4 (KD4) received the *n*-hexane fraction at a dose of 125 mg/kgBW, dose group 5 (KD5) received the ethyl acetate fraction at a dose of 125 mg/kgBW, and dose group 6 (KD6) received the butanol fraction at a dose of 125 mg/kgBW. The diabetic animals were treated according to their respective group assignments. The treatments were administered 30 min prior to glucose loading as a single oral dose. Thirty minutes after treatment, each experimental animal, except those in the normal control group, was orally administered a glucose solution at a dose of 2 g/kg body weight. Blood glucose levels were measured at 30, 60, 90, and 120 min after glucose administration. Blood samples were collected from the lateral tail vein and analyzed using a glucometer (Autocheck®) [24]. The blood glucose level data were subsequently used to calculate the AUC and the percentage reduction in blood glucose levels. The animals that had been used were subsequently euthanized by placement into a killing jar containing cotton saturated with chloroform. The animals

were monitored and remained in the jar until death was confirmed [25].

The area under the curve (AUC) value was determined to evaluate changes in blood glucose levels for each treatment group. The AUC was calculated using the formula 1 [26].

$$AUC = \frac{KGDt_1 + KGDt_2}{2} \times (t_2 - t_1) \quad (1)$$

Where,

AUC : Area under the curve;

$KGDt_1$: Initial blood glucose level (mg/dL)

$KGDt_2$: Final blood glucose level (mg/dL);

t_1 : Time of initial blood glucose measurement (min);

t_2 : Time of final blood glucose measurement (min)

The percentage reduction in blood glucose levels was calculated using the formula 2 [26].

$$\%PKGD = \frac{AUC_{KN} - AUC_P}{AUC_{KN}} \times 100\% \quad (2)$$

Where, %PKGD : Percentage reduction in blood glucose level; AUC (KN) : AUC of the negative control group; AUC (P) : AUC of the treatment group.

***In Vitro* Antioxidant Assay**

The antioxidant activity in this study was evaluated using the ABTS radical method. The ABTS stock solution was mixed with 5 mL of potassium persulfate solution to generate ABTS radical cations. The resulting mixture was then kept in the dark for 12–16 h at a temperature of 22–24°C, producing a dark blue ABTS radical solution [27]. Sample stock solutions (1000 ppm) were prepared by weighing 10 mg each of the ethanolic extract and concentrated fractions of *Arcangelisia flava* stem, which were then dissolved in 10 mL of 96% ethanol. From these stock solutions, a series of concentrations were prepared as follows: *Arcangelisia flava*

ethanolic extract at 10, 20, 30, 40, and 50 ppm; *n*-hexane fraction at 40, 60, 80, 100, and 120 ppm; ethyl acetate fraction at 5, 7.5, 10, 12.5, and 15 ppm; and butanol fraction at 5, 10, 15, 20, and 25 ppm [28]. The vitamin C stock solution was prepared by dissolving 10 mg of vitamin C in 10 mL of 96% ethanol. From this stock solution, a series of concentrations were prepared at 2.5, 5, 7.5, 10, and 12.5 ppm [28]. A total of 1 mL from each sample concentration series and 1 mL from each standard concentration series were mixed with 1 mL of ABTS solution.

The mixture was then adjusted to a final volume of 5 mL using 96% ethanol, homogenized, and incubated at room temperature for 10 min (operating time). The absorbance was measured at a wavelength of 745 nm using a UV-Vis spectrophotometer [28]. The inhibitory concentration (IC₅₀) was determined by analyzing the relationship between the percentage of inhibition and the sample concentration, represented as a calibration curve. The percentage of inhibition (% inhibition) was calculated using the formula 3.

$$\% \text{Inhibition} = [A_{\text{control}} - A_{\text{sample}}] / A_{\text{control}} \times 100 \quad (3)$$

The percentage of inhibition values were used to calculate the IC₅₀ value using formula 4.

$$\text{IC}_{50} (\text{ppm}) = \frac{50-a}{b} \quad (4)$$

where (x) is the sample concentration (ppm or µg/mL), (a) is the intercept of the regression equation, and (b) is the slope of the regression line.

The strength of antioxidant activity based on the IC₅₀ value is generally classified into four categories: very strong (IC₅₀ < 50 ppm), strong (IC₅₀ = 50–100 ppm), moderate (IC₅₀ = 100–150 ppm), and weak (IC₅₀ > 150 ppm) [29].

Network pharmacology

The bioinformatics analysis was conducted *in silico* using an ASUS laptop with an Intel Core i3 7th Generation processor. In this study, compounds numbered 7 and 17 identified through GC-MS/MS analysis were selected for network pharmacology evaluation due to their chemical classification as phenolic derivatives and alkaloid compounds. These classes of secondary metabolites are widely reported to exhibit antidiabetic properties through multiple mechanisms. The compound 7 and 17 canonical SMILES were obtained from PubChem

(<https://pubchem.ncbi.nlm.nih.gov/>)

(accessed on October 30, 2025). Target proteins of these bioactive small molecules were predicted using SwissTargetPrediction

(<http://www.swisstargetprediction.ch/>)

(accessed on October 30, 2025), while diabetes mellitus-related target proteins were retrieved from GeneCards (<https://www.genecards.org/>) (accessed on October 30, 2025). The results from both databases were combined and analyzed using a Venn diagram generated through Venny

(<https://bioinfogp.cnb.csic.es/tools/venny/>)

(accessed on October 30, 2025) to identify overlapping proteins associated with both the metabolites and diabetes mellitus. The intersected proteins were then analyzed using ShinyGO

(<http://bioinformatics.sdstate.edu/go74/>)

(accessed on October 30, 2025) focusing on Kyoto Encyclopedia of Genes and Genomes (KEGG) pathways to obtain the top 50 enriched biological mechanisms, and the Gene Ontology (GO) terms were visualized through an enrichment bubble plot. Furthermore, the target proteins were imported into STRING-DB (<https://string-db.org/>) (accessed on October 30, 2025) to construct a protein-protein interaction (PPI) network related to diabetes mellitus, and

subsequently analyzed using the CytoHubba plugin in Cytoscape version 3.10 to identify the genes based on the Maximal Clique Centrality (MCC) algorithm [30].

Data Analysis

The blood glucose levels were statistically analyzed using the ANOVA, and posthoc LSD. The analysis was conducted at a 95% confidence level ($\alpha = 0.05$) using the IBM Statistical Package for the Social Sciences (SPSS®) software version 21.

Result and Discussion

Chemical compound from *Arcangelisia flava* Fraction using GC-MS

The chemical constituents of the n-hexane fraction of *Arcangelisia flava* were analyzed using Gas Chromatography–Mass Spectrometry (GC–MS). The GC–MS analysis identified 18 volatile compounds (Table 1), with the corresponding chromatogram presented in Figure 1. The major classes of compounds in the n-hexane fraction of

Arcangelisia flava were presumed to be fatty acid derivatives (6 compounds), followed by aromatic hydrocarbons (5 compounds), alcohols (2 compounds), and one compound each from the terpenoid, phenolic, and alkaloid groups (Table 1). In a separate study, the chemical composition of *Arcangelisia flava* wood collected from the Philippines was also analyzed, identifying a total of 64 compounds. Among them, two compounds that are ethylbenzene and o-xylene, were found to be consistent with the GC–MS results obtained in the present study [31].

The volatile compounds present in the n-hexane fraction of *Arcangelisia flava* are presumed to possess pharmacological activity. The fatty acid derivative with the highest probability (prob%) was identified as Hexadecanoic acid ethyl ester (16.9%). This compound has also been detected in *Nigella sativa* seeds and has been reported to exhibit pharmacological potential, particularly by playing a role in neuroprotective effects through the inhibition of EGR1[32].

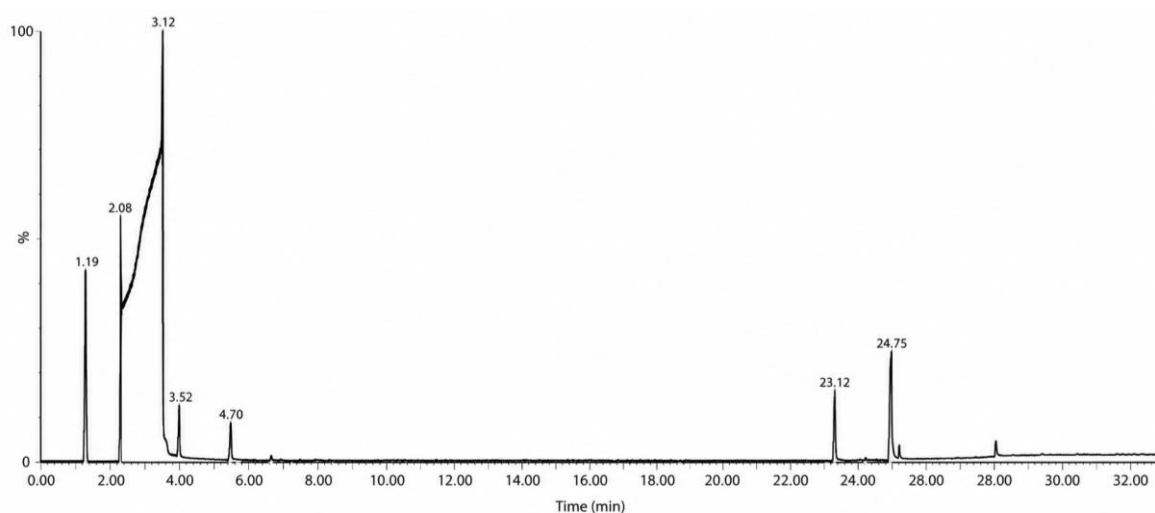


Figure 1. GC–MS Spectrum of the n-Hexane Fraction of *Arcangelisia flava* from Southeast Sulawesi

In addition, in a separate study, hexadecanoic acid was reported to be present in *Codiaeum variegatum* and is suggested to exert antidiabetic effects

through the inhibition of glucosidase and amylase enzymes [33]. The alkaloid compound Strychane, 1-acetyl-20 α -hydroxy-16-methylene- was identified in the fruit of

Cassia fistula and is presumed to contribute to the plant's antibacterial and antifungal effects [34]. In a separate study, *Strychane*, 1-acetyl-20 α -hydroxy-16-methylene-, has been reported to be present in *Strychnos nux-vomica* [35], and is suggested to contribute to its antidiabetic effects [36]. The similarity

in active compounds, namely Hexadecanoic acid ethyl ester and Strychane, 1-acetyl-20 α -hydroxy-16-methylene-, identified in *Arcangelisia flava*, is presumed to contribute to other potential pharmacological effects, including antidiabetic activity.

Table 1. The Phytochemical compound Profile of *Arcangelisia flava* n-hexane Fraction

Compound number	RT	MW	Match	Prob (%)	Formula	Chemical compound name	Classes of compounds
1	3.516	92	843	13.5	C ₇ H ₈	Spiro[2,4]hepta-4,6-diene	Aromatic hydrocarbons
2	4.702	104	557	6.89	C ₅ H ₁₂ O ₂	2-Methylbutane-1,4-diol	Aromatic hydrocarbons
3	6.227	106	870	41.9	C ₈ H ₁₀	Ethylbenzene	Aromatic hydrocarbons
4	6.502	106	839	13.2	C ₈ H ₁₀	o-Xylene	Aromatic hydrocarbons
5	7.149	106	770	12.8	C ₈ H ₁₀	p-Xylene	Aromatic hydrocarbons
6	7.535	142	606	4.11	C ₈ H ₁₄ O ₂	6-Hepten-3-one, 5-hydroxy-4-methyl-	Ketones and alcohols
7	17.781	206	729	10.8	C ₁₃ H ₁₈ O ₂	4-Hydroxy-3,5-diisopropylbenzaldehyde	Phenolic aldehyde
8	18.804	204	634	5.68	C ₁₀ H ₂₀ O ₂ S	3-n-Hexylthiolane, S,S-dioxide	Sulfur compounds
9	19.973	252	617	3.06	C ₁₅ H ₂₄ O ₃	Ageratriol	Terpenes
10	21.073	214	616	3.81	C ₁₄ H ₃₀ O	7-Tetradecanol	alcohols
11	21.947	280	535	4.94	C ₁₈ H ₃₂ O ₂	17-Octadecynoic acid	Non-aromatic hydrocarbons
12	22.102	200	533	4.24	C ₁₂ H ₂₄ O ₂	8-Methylnonanoic acid, ethyl ester	Fatty acids derivate
13	23.12	284	724	16.9	C ₁₈ H ₃₆ O ₂	Hexadecanoic acid, ethyl ester	Fatty acids derivate
14	24.711	308	821	6.71	C ₂₀ H ₃₆ O ₂	Ethyl 9.cis.,11.trans.-octadecadienoate	Fatty acids derivate
15	24.764	282	748	5.07	C ₁₈ H ₃₄ O ₂	Cis-accenic acid	Fatty acids derivate
16	24.999	298	682	12.6	C ₁₉ H ₃₈ O ₂	Ethyl 14-methyl-hexadecanoate	Fatty acids derivate
17	28.335	338	521	10.6	C ₂₁ H ₂₆ N ₂ O ₂	Strychane, 1-acetyl-20 α -hydroxy-16-methylene-	Alkaloid
18	30.251	312	472	3.17	C ₂₀ H ₄₀ O ₂	n-Propyl 14-methyl-hexadecanoate	Fatty acids derivate

Antidiabetic activity

In this study, a total of 36 mice were used and induced to develop diabetes mellitus using the STZ-NA model. Streptozotocin (STZ) serves as a diabetogenic agent that generates free radicals and is toxic to pancreatic β -cells, leading to impaired insulin secretion and hyperglycemia [37]. However, the cytotoxic effect of STZ on β -cells is highly destructive and closely resembles the pathological features of type 1 diabetes in humans [38]. This condition is undesirable for modeling type 2 diabetes mellitus; therefore, a combination with nicotinamide (NA) is required to mitigate the cytotoxic effects of STZ. Nicotinamide (NA), a

derivative of vitamin B3, possesses antioxidant properties and can reduce the cytotoxic action of STZ. The STZ-NA-induced type 2 diabetes model allows pancreatic β -cells to avoid extensive destruction and produces a diabetic condition characterized by insulin deficiency without insulin resistance. This model is marked by stable, moderate hyperglycemia associated with approximately 60% loss of β -cell function [19], [38]. In this study, the dose of streptozotocin (STZ) used ranged from 45 to 65 mg/kgBW, while the dose of nicotinamide (NA) ranged from 60 to 290 mg/kgBW. [19]. The blood glucose profile obtained from the experimental results is presented in **Table 2**.

Table 2. Profile of Blood Glucose Levels of Experimental Animals During the OGTT

Group	Average Blood Glucose Levels of Test Animals at Each Time Point (t) $\pm$ SD (n = 4)									
	t ₀		t ₃₀		t ₆₀		t ₉₀		t ₁₂₀	
KN	167.3	$\pm 3^b$	95.0	± 28.6	112.6	± 7.3	79.6	± 9.6	81.0	± 5
K-	194.0	$\pm 6^a$	193.3	± 4.1	194.6	± 9.2	204.6	± 15.8	218.6	± 15.5
K+	184.3	± 5	112.0	± 7	116.6	± 10.7	95.0	± 18.3	70.6	± 14.5
KD1	202.0	± 22.3	147.3	$\pm 45.5^c$	99.0	$\pm 15.1^{b,c}$	79.6	$\pm 7.5^{b,c}$	77.6	$\pm 9.6^{b,c}$
KD2	191	± 3.4	151.0	$\pm 34.2^c$	127.3	$\pm 21.9^c$	115.0	$\pm 15.1^{b,c}$	74.6	$\pm 12.5^{b,c}$
KD3	202.6	± 8.9	107.6	$\pm 30^c$	101	$\pm 36.8^c$	74	$\pm 4.5^{b,c}$	67	$\pm 2.6^{b,c}$
KD4	208	$\pm 25.16^a$	151	$\pm 16.77^{a,c}$	137.7	$\pm 12.89^{b,c}$	82.7	$\pm 9.01^{b,c}$	76	$\pm 11.50^{b,c}$
KD5	117.3	$\pm 38.97^{a,b}$	102.7	$\pm 16.50^{b,c}$	82	$\pm 16.50^{b,c}$	72	$\pm 15.13^{b,c}$	121	$\pm 16.09^{b,c}$
KD6	224.3	$\pm 16.17^a$	140	$\pm 29.51^{b,c}$	131	$\pm 29.51^{b,c}$	96	$\pm 2^{b,c}$	81.7	$\pm 4.50^{b,c}$

Where, KN : Normal Control; K- : Negative Control; K+ : Positive Control; KD 1, 2, and 3 : Treatment groups administered the extract at doses of 125, 250, and 500 mg/kgBW, respectively; KD 4, 5, and 6 : Treatment groups administered the *n*-hexane, ethyl acetate, and butanol fractions, respectively, at a dose of 125 mg/kgBW; a : Significantly different from the normal control group ($p < 0.05$); b : Significantly different from the negative control group ($p < 0.05$); c : Not significantly different from the positive control group ($p > 0.05$)

Administration of the *Arcangelisia flava* extract and its fractions demonstrated a pharmacological effect in reducing the blood glucose levels (BGL) of the animals. A decrease in BGL was observed in the positive control group and in the treatment groups receiving *Arcangelisia flava* samples, starting from the 30th to the 120th min. The BGL

values of the treatment groups between 60 and 120 min showed a significant difference ($p < 0.05$) compared to the negative control group (Table 2). This finding indicates that the administration of the extract and fractions effectively reduced the BGL of the animals. The percentage of BGL reduction was subsequently calculated, showing the

highest decrease in the group treated with ethanolic extract at a dose of 500 mg/kgBW, followed by the ethyl acetate, *n*-hexane, and butanol fractions at 125 mg/kgBW, respectively (Table 3) [40]. In this study, we also calculated the Area Under the Curve (AUC) using the blood glucose level data. The AUC value is inversely proportional to the antidiabetic activity of a drug, where a lower AUC indicates more effective utilization of the compound in reducing blood glucose levels. Thus, the smaller the AUC value, the greater the efficacy of the substance in

lowering blood glucose concentration [41]. In this study, the lowest AUC value was observed in the group treated with the ethanolic extract at a dose of 500 mg/kgBW, followed by the positive control group and the groups treated with the ethyl acetate, *n*-hexane, and butanol fraction, respectively (Table 3). These results indicate that a lower AUC value corresponds to better blood glucose control in the animals, which can be attributed to the administration of the extract, glibenclamid, and the fractions.

Table 3. Area Under the Curve (AUC) and Percentage Reduction in Blood Glucose Levels of Test Animals After Treatment

Treatment group	Area under curve (AUC)	Percentage Reduction in Blood Glucose Levels (%)
KN	3086	48.49
K-	5992	0.00
K+	3383	43.53
KD1	3482	41.88
KD2	3946	34.14
KD3	2981	50.25
KD4	3856	34.96
KD5	3394	42.82
KD6	3903	34.28

Where, KN : Normal Control; K- : Negative Control; K+ : Positive Control; KD 1, 2, and 3 : treatment groups administered the extract at doses of 125, 250, and 500 mg/kgBW, respectively; KD 4, 5, and 6 : treatment groups administered the *n*-hexane, ethyl acetate, and butanol fractions, respectively, at a dose of 125 mg/kgBW

The efficacy of *Arcangelisia flava* to reduce the BGL can be observed from the differences in BGL between the positive control and the treatment groups with extract and fractions. All samples exhibited a percentage reduction in BGL comparable to the positive control. Notably, the group treated with the ethanolic extract at 500 mg/kgBW showed a lower AUC and a higher percentage reduction in blood glucose compared to the positive control (Table 3). Statistical analysis also indicated no significant difference ($p > 0.05$) in blood glucose levels between the positive control and the treatment groups. These findings

suggest that the administration of the extract and fractions effectively lowers blood glucose levels in the animals, with a hypoglycemic effect produced comparable glucose-lowering effect to glibenclamide in this OGTT model.

The antihyperglycemic activity of *Arcangelisia flava* stems is closely related to the bioactive compounds. The stems of *Arcangelisia flava* have been reported to contain berberine (Karim et al., 2020), which is known to inhibit the enzyme α -glucosidase, and reduces glucose absorption in the intestine. Molecular docking studies have also shown

that berberine exhibits a low binding affinity value toward dipeptidyl peptidase-IV (DPP-IV), indicating strong interaction with this receptor [13]. In a separate study, *Arcangelisia flava* was also reported to contain palmatine, another bioactive alkaloid [42]. This compound is known to exhibit strong inhibitory activity against α -amylase, while showing weaker inhibition toward α -glucosidase and DPP-4 [43]. The GC-MS analysis of the *n*-hexane fraction in this study, we identified the compound hexadecanoic acid, ethyl ester, which is known to possess antidiabetic effects. [44]. The presence of this compound in *Arcangelisia flava* is presumed to play a key role in reducing blood glucose levels of the animals in this study.

The antidiabetic potential of *Arcangelisia flava* is also associated with its antioxidant effects. The relationship between free radicals and the development of diabetes mellitus continues to be explored, particularly at the molecular level. One study described several mechanisms linking free radicals to diabetes, including mitochondrial ROS; non-mitochondrial ROS such as NAD(P)H oxidase (NOX), xanthine oxidase (XO), uncoupled nitric oxide synthase (NOS), cyclooxygenase-2 (COX-2), and endoplasmic reticulum (ER) stress; carbonyl stress; as well as the Warburg effect (aerobic glycolysis) and cell proliferation [15]. Therefore, the use of antioxidants is associated with the prevention of diabetes mellitus. *Arcangelisia flava* contains multiple chemical compounds that may act as both antidiabetic and antioxidant agents. Among them, palmatine, reported in *Arcangelisia flava*, has been shown to effectively neutralize DPPH free radicals and exhibit strong activity in non-enzymatic SOD mimic systems [45]. Other studies have also demonstrated that palmatine possesses antioxidant and antiglycation properties, with its mechanism of action believed to involve the inhibition of

free radical formation and the reduction of reactive carbonyl compounds [46]. Berberine has been shown to enhance the body's natural antioxidant defenses, including superoxide dismutase (SOD), catalase (CAT), and glutathione peroxidase (GPx) [47]. To support these findings, in the present study, the antioxidant activity of *Arcangelisia flava* from Southeast Sulawesi was evaluated using the ABTS assay.

Antioxidant Activity

The antioxidant activity was analyzed using both the extract and its fractions. The assay employed was the 2,2'-azino-bis(3-ethylbenzothiazoline-6-sulfonic acid) (ABTS) method. Antioxidants react with ABTS through electron transfer, converting the colored radical form into its colorless reduced form. The degree of this reduction correlates with the antioxidant capacity of the samples. As commonly noted, the ABTS assay is considered more sensitive than DPPH and FRAP assays due to its reaction kinetics and the nature of the radical species involved [48].

Table 4. IC₅₀ values of ethanolic extract and Fractions of *Arcangelisia flava* based on the ABTS Method

Samples	IC ₅₀ (ppm)
Vitamin C	8.00
Ethanol extract	49.80
<i>n</i> -hexane fraction	110.25
Ethyl acetate fraction	10.20
Butanol fraction	18.44

Based on the results of the ABTS antioxidant assay, the ethyl acetate fraction of *Arcangelisia flava* stems exhibited the highest antioxidant potential, with an IC₅₀ of 10.20 ppm, which is close to the IC₅₀ of Vitamin C (8.00 ppm) used as the positive control. The butanol fraction also demonstrated strong antioxidant activity, with an IC₅₀ of 18.44 ppm. In contrast, the *n*-hexane fraction

showed moderate antioxidant activity, with an IC_{50} greater than 100 ppm. These results indicate that the active antioxidant compounds are more soluble in semi-polar solvents, which are capable of extracting aglycone flavonoids, such as polyphenols present in the extract. Phenolic compounds function as antioxidants due to their ability to regenerate reactive oxygen species, as their aromatic rings contain hydroxyl groups that act as electron donors, stabilizing and neutralizing free radicals. Flavonoids, being derivatives of polyphenols, also play a crucial role in determining antioxidant activity. Together, these compounds contribute significantly to the overall antioxidant potential of the extract and its fractions.

This finding also suggests that the *n*-hexane fraction contains relatively low levels of polar antioxidant compounds, which are typically responsible for radical-scavenging activity. However, despite its limited antioxidant potential, the *n*-hexane fraction was selected for further GC-MS/MS analysis due to its ability to extract nonpolar and semi-polar constituents, including fatty acids, terpenoids, and alkaloid-related compounds [49], which may exert biological activities through mechanisms independent of antioxidant effects. Moreover, antidiabetic activity is not exclusively mediated by antioxidant capacity but may involve alternative pathways such as enzyme inhibition, insulin signaling modulation, and glucose metabolism regulation [50]. Therefore, the chemical constituents identified in the *n*-hexane fraction were prioritized for network pharmacology analysis *in silico* to explore their potential interactions with diabetes-related molecular targets. This approach allows the identification of multi-target mechanisms that may underlie the antidiabetic potential of nonpolar bioactive compounds present in the extract.

Network Pharmacology

The compounds identified by GC-MS, specifically compounds 7 and 17, were further analyzed for target protein identification (Figure 2). The selection of compounds 7 and 17 was based on their classification as phenolic and alkaloid derivatives, respectively. Compounds from the phenolic and alkaloid classes have been widely reported to exhibit antidiabetic effects. Compound 7 is a phenolic aldehyde derivative, a group of compounds known to reduce blood glucose levels and enhance insulin secretion. Collectively, these pharmacological properties provide a strong rationale for selecting compounds 7 and 17 for further investigation of their potential antidiabetic activity [51].

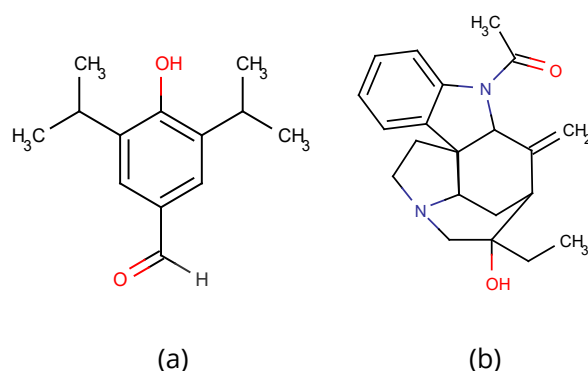


Figure 2. The two compounds used in the pharmacological analysis. (a) compound 7, 4-Hydroxy-3,5-bis(isopropyl)benzaldehyde, and (b) compound 17, Strychane, 1-acetyl-20 α -hydroxy-16-methylene-. The chemical structures of these compounds were drawn using MarvinSketch® 5.2.5.1.

In addition, compound 17, identified as *Strychane, 1-acetyl-20 α -hydroxy-16-methylene*, has been reported to be present in *Strychnos nux-vomica* [35], and is suggested to contribute to its antidiabetic effects [36]. Data on the target proteins of these compounds were obtained from SwissTarget, while disease-related target proteins were retrieved from GeneCards.

Both datasets were then analyzed using the Draw Venn Diagram tool. The analysis revealed 80 overlapping target proteins between the targets of compounds in the *n*-hexane fraction of *Arcangelisia flava* and proteins associated with type 2 diabetes mellitus (Figure 3).

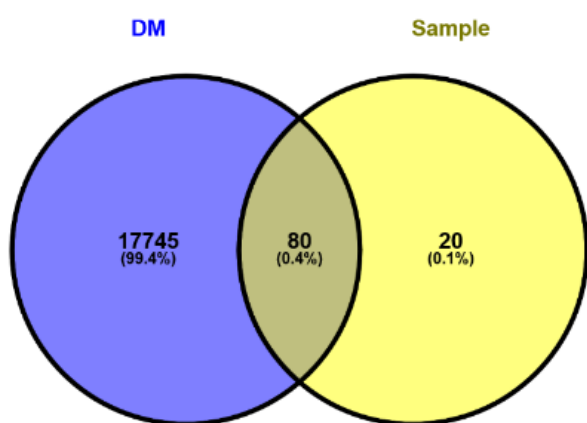


Figure 3. Overlay Analysis Using a Venn Diagram. A total of 100 target proteins were associated

with compounds from *Arcangelisia flava*, while 17,745 proteins are involved in diabetes mellitus. The intersection revealed 80 target proteins of *Arcangelisia flava* compounds that are also implicated as targets in type 2 diabetes mellitus. These 80 proteins were subsequently analyzed using CytoHubba to identify the central proteins with the greatest influence on the therapeutic effects of the compounds in the *n*-hexane fraction of *Arcangelisia flava*. The proteins were ranked based on Maximal Clique Centrality (MCC). MCC analysis helps determine the most critical proteins within the pharmacological network by identifying groups of proteins that form closed network clusters. Proteins within the MCC were then evaluated according to their centrality in subnetworks, which measures the importance of a protein in maintaining or influencing connections within the network [52].

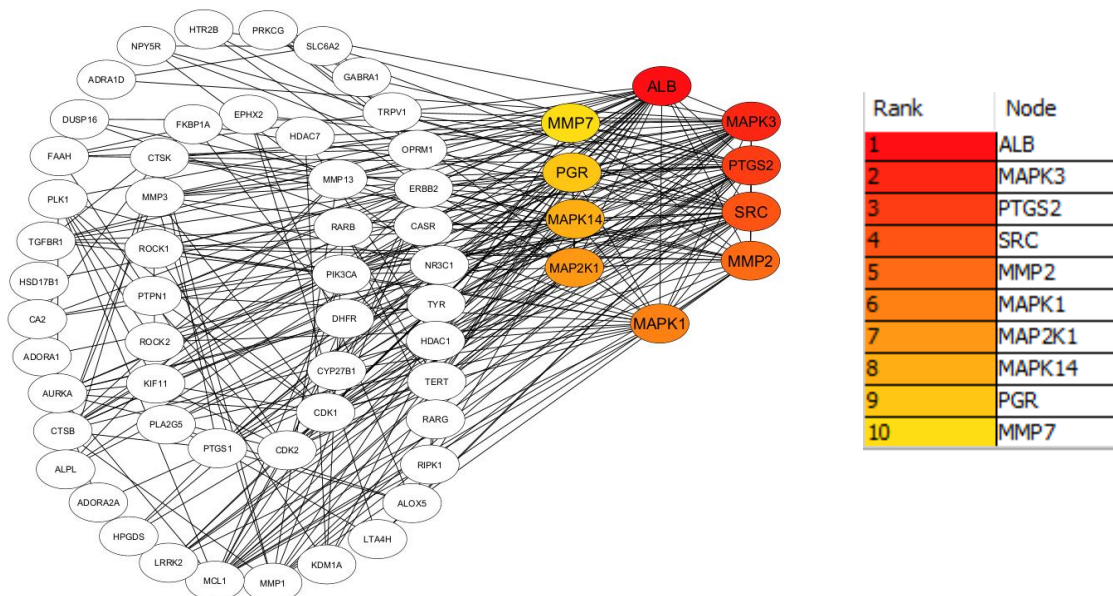


Figure 4. Visualization of protein-protein interactions (PPI) targeting the bioactive compounds of the *n*-hexane fraction of *Arcangelisia flava* against type 2 diabetes mellitus (T2DM). The analysis was performed using Cytoscape 3.10 with a confidence value of 0.8 to identify the ten key proteins based on Maximal Clique Centrality (MCC) using the CytoHubba plugin.

Pharmacological analysis identified ten central proteins with the highest scores, namely ALB, MAPK3, PTGS2, SRC, MMP2, MAPK1, MAP2K1, MAPK14, PGR, and MMP7

(Figure 4). These findings were further validated through KEGG pathway analysis. The 80 target proteins were analyzed to determine their mechanistic pathways

based on KEGG data. The analysis revealed that the most significant pathway associated with type 2 diabetes mellitus (T2DM) for the *n*-hexane fraction of *Arcangelisia flava* is the AGE-RAGE signaling pathway in diabetic complications (Figure 5). Other signaling pathways not included in the top 50 KEGG

pathways included the insulin signaling pathway. The proteins responsible for the AGE-RAGE signaling pathway were identified using STRING-DB (Table 5). Six proteins were found to play key roles in this pathway are MAPK1, MMP2, MAPK14, MAPK3, PIK3CA, and TGFBR1.

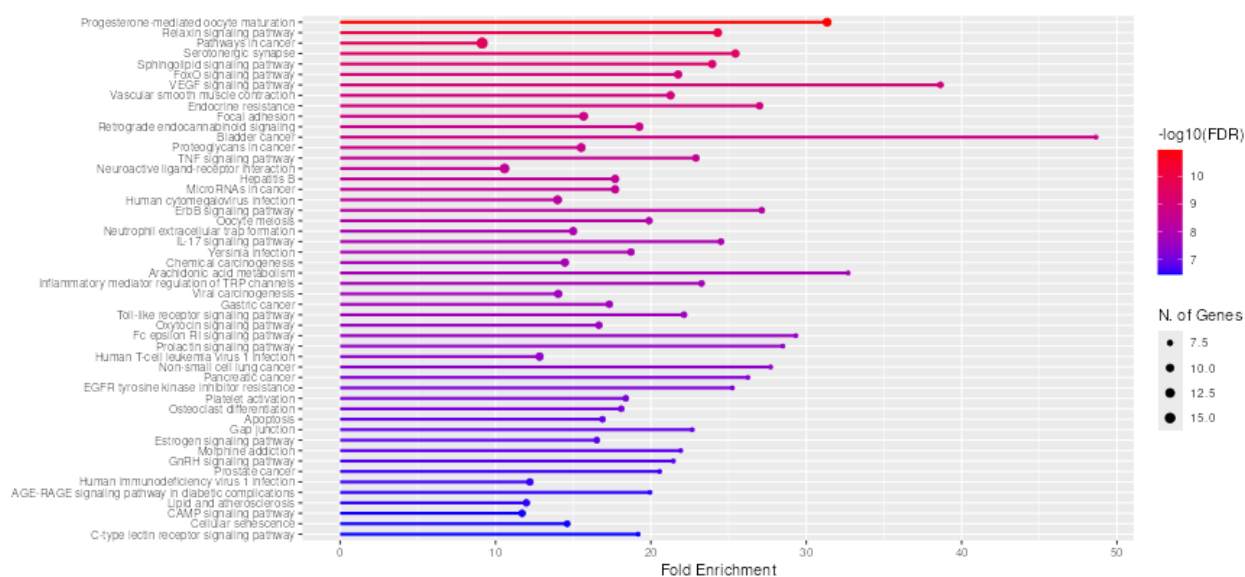


Figure 5. Annotation of the top 50 KEGG pathways targeted by *Arcangelisia flava*, performed using the ShinyGO web platform

The AGE-RAGE signaling pathway has been extensively studied. Patients with type 2 diabetes mellitus (T2DM) have been shown to exhibit significantly higher concentrations of Advanced Glycation End Products (AGEs) compared to non-diabetic populations. AGEs are formed throughout life due to elevated circulating glucose levels and other reducing sugars, such as galactose and fructose, which react with amino groups on proteins to form Schiff bases. These intermediates then enter the polyol pathway to generate AGEs or undergo degradation. The resulting AGEs interact with Receptors for Advanced Glycation End Products (RAGEs), transmembrane proteins belonging to the immunoglobulin family. RAGE expression increases in response to elevated circulating AGE levels. Upon AGE-RAGE binding, RAGE

activates PKC- ζ (protein kinase C zeta), which subsequently triggers downstream signaling cascades via p38 mitogen-activated protein kinase (MAPK), transforming growth factor- β (TGF- β), and nuclear factor κ B (NF- κ B). This activation stimulates signaling pathways that can induce diabetes-related complications, particularly in the vascular system [53].

Conclusion

In conclusion, the extract and fractions of *Arcangelisia flava* stem bark has the potential to lower blood glucose levels and scavenge free radicals. The *n*-hexane fraction is presumed to exert its antidiabetic effect through the inhibition of the AGE-RAGE signaling pathway, which plays a critical role in diabetic complications. This study is limited by its reliance on in silico network

pharmacology approaches, which are inherently dependent on predictive databases and computational algorithms. Consequently, the identified compound–target interactions may not fully represent biological complexity under physiological conditions. In addition, only selected compounds identified by GC–MS/MS were included, potentially overlooking other bioactive constituents and synergistic effects within the extract. Future studies should prioritize experimental validation of the predicted targets and pathways through in vitro and in vivo assays to confirm antidiabetic efficacy and mechanistic relevance. Expanding phytochemical coverage and integrating pharmacokinetic and toxicity evaluations will be essential to advance the extract toward translational and clinical applications. Further studies are required to isolate the active compounds and validate their mechanisms of action using in vitro and in vivo models.

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Author Contributions

Conceptualization, Nurramadhani A. Sida and Henny Kasmawati.; Methodology, Nurramadhani A. Sida.; Software, ; Validation, Henny Kasmawati, Hasnawati.; Formal Analysis, Rifa'atul Mahmudah.; Investigation, Nurramadhani A. Sida.; Resources, Nurramadhani A. Sida; Data Curation, Rifa'atul Mahmudah; Writing – Original Draft Preparation, Nurramadhani A. Sida, Hasnawati; Writing – Review & Editing, Nurramadhani A. Sida.; Visualization, Nurramadhani A. Sida.; Supervision, Henny Kasmawati.; Project Administration, Rifa'atul

Mahmudah.; Funding Acquisition, Nurramadhani A. Sida.

Conflict of Interest

The authors declare no conflict of interest.

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