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Indonesian Journal of Fundamental and Applied Chemistry

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Antidiabetic Activity and Chemical Compound Analysis of Fractions of *Leucas lavandulifolia* Leaves

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Abstract

Leucas lavandulifolia is a traditional medicinal plant used to treat rheumatism, skin diseases, wounds, diabetes, and migraines. This research aimed to test the antidiabetic activity of *L. lavandulifolia* leaf fractions and to identify the chemical content of the selected column fraction. Fractionation was performed using the graded extraction method using *n*-hexane, ethyl acetate, and methanol. The antidiabetic activity was assessed by α-glucosidase inhibition method, and the chemical composition of selected fraction was analyzed using the GC-MS method. The result showed that the ethyl acetate fraction provided highest antidiabetic activity (IC_{50} = 4.98 µg/mL) compared to other fractions and higher than positive control acarbose (IC_{50} = 67.07 µg/mL). Separation of the ethyl acetate fraction showed that subfractions F6.3 and F6.5 showed the simplest spot pattern. Using GC-MS, identification of the chemical content revealed that subfraction F6.3 contained the main component, a naphthalenepropanal derivative (17.21%), and subfraction F6.5 contained the main compound, a fatty acid. Subfractions F6.3 and F6.5 also showed antidiabetic activities with IC_{50} values of 17.3 and 36.72 µg/mL, respectively, with a strong category. This data indicates that the ethyl acetate fraction of *L. lavandulifolia* leaves can be developed as a source of antidiabetic compounds.

Keywords: *α-glucosidase, Leucas lavandulifolia, ethyl acetate fraction, antidiabetic*

Article Info

Received 28 July 2025
Received in revised 30 September 2025
Accepted 4 October 2025
Available Online 29 October 2025

Abstrak (Indonesian)

Leucas lavandulifolia merupakan salah satu obat tradisional yang telah digunakan untuk pengobatan rematik, penyakit kulit, luka, diabetes dan pengobatan migrain. Penelitian ini bertujuan untuk menguji aktivitas antidiabetes fraksi daun *L. lavandulifolia* dan mengidentifikasi kandungan kimia fraksi kolom terpilih. Fraksinasi dilakukan dengan metode ekstraksi bertingkat menggunakan pelarut n-heksana, etil asetat, metanol, Pengujian aktivitas antidiabetes menggunakan metode penghambatan α-glukosidase dan analisa komposisi kandungan kimia fraksi terpilih dilakukan dengan menggunakan metode GC-MS. Hasil menunjukkan fraksi etil asetat memberikan aktivitas antidiabetes paling tinggi (IC_{50} = 4,985 µg/mL) dibandingkan fraksi lainnya dan lebih tinggi dibandingkan dengan kontrol positif akarbosa (IC_{50} = 67,07 µg/mL). Pemisahan fraksi etil asetat menunjukkan subfraksi F6.3 dan F6.5 menunjukkan pola noda paling sederhana. Identifikasi kandungan kimia dengan GC-MS menunjukkan subfraksi F6.3 mengandung komponen utama derivat naftalenpropanal (17,21%) dan subfraksi F6.5 dengan komponen utama asam lemak. Sub fraksi F6.3 dan F6.5 juga menunjukkan aktivitas antidiabetes dengan nilai IC_{50} masing 17,3 dan 36,72 µg/mL dengan kategori sangat kuat yang mengindikasikan fraksi etil asetat daun *L. lavandulifolia* potensial untuk dikembangkan sebagai sumber senyawa antidiabetes.

Kata Kunci: *α-glucosidase, Leucas lavandulifolia, fraksi etil asetat, antidiabetes*

INTRODUCTION

Indonesia boasts a rich biodiversity encompassing numerous medicinal plant species, many of which remain largely unexplored for their potential benefits. Many among them have not yet been discovered scientifically despite their widespread used in traditional medicine [1]. One is *Leucas lavandulifolia* (Lamiaceae), known locally as lenglengan. Communities have traditionally utilized their leaves to treat various diseases, such as rheumatism, skin disorders, fever, respiratory disorders, and especially diabetes [2-4].

Modern pharmacological research supports this traditional use. *L. lavandulifolia* leaves are known to possess various biological activities. Information on the biological activities of the leaves is reported to be active as anti-inflammatory, antimicrobial, anti-ulcer, antidiabetic, antitussive, antioxidant, and wound healing [5-7]. The Chemical content analysis contains acacetin, chrysoeriol, linifoliside, and p-hydroxybenzoic acid [2,8,9]. Furthermore, based on a literature study, scientific information on the antidiabetic activity of the leaf extract of the plant *L. lavandulifolia* has not been found, while its traditional use for diabetes therapy is quite widespread. However, there is insufficient scientific information regarding the specific antidiabetic activity of *L. lavandulifolia* leaf extract. On the other hand, the global need for antidiabetic agents is high. Therefore, further research is needed to explore the potential of *L. lavandulaefolia* leaf extract.

This research aims to test the antidiabetic activity of *L. lavandulifolia* leaf fractions using the α-glucosidase enzyme inhibition method. The leaf fraction showing the highest activity was separated using various chromatography techniques. The potentially active subfraction was subsequently analyzed for its chemical content using the GC-MS method. The results of this research will serve as the basis for developing phytopharmaceuticals for the *L. lavandulifolia* plant as phytopharmaceutical preparations for antidiabetic therapy.

MATERIALS AND METHODS

Material

Research Materials: Methanol, *n*-hexane, ethyl acetate, acetone, chloroform (Sigma), silica gel GF254 TLC plates, cerium (IV) sulphate, and sulfuric acid (Merck, Germany); α-glucosidase (Merck), p-nitrophenyl α-*D*-glucopyranoside (pNPG), and acarbose (Sigma-Aldrich). Analytical instruments included a rotary evaporator (Model RE-2010VN, Yamato), GC-MS system (Agilent Technologies 7890B/5977B), microplates (Biologix 800TS), and an ELISA microplate reader (Model 4800, EQUITRON).

Methods

Sample collection and preparation

Fresh leaves of *Leucas lavandulifolia* were collected from Ogan Ilir Regency, South Sumatra, Indonesia. The leaves were rinsed with distilled water and subsequently air-dried at room temperature (25 ± 2 °C) in a shaded area. The dried material was then mechanically ground (using a 40-mesh sieve) until a powder of *L. lavandulifolia* dried leaves was obtained.

Extraction of L. lavandulifolia

Leaf powder (1 kg) was extracted using the maceration method with solvents of graded polarity (n-hexane, ethyl acetate, and methanol). Extraction with each solvent was performed with three repetitions (3 × 24 hours), then filtered, and the collected filtrate was concentrated using a rotary evaporator at 60 °C to obtain concentrated extracts of each solvent: *n*-hexane, ethyl acetate, and methanol, which were subsequently designated as fractions. The yield value of each fraction was then calculated using the formula:

$$\%\ \text{Extract yield} = \frac{\text{Extract weight}}{\text{Simplicia weight}} \times 100\% \quad \ldots\ldots (1)$$

Antidiabetic activity assay using the α-glucosidase inhibition method

The antidiabetic activity test of each fraction was conducted based on the α-glucosidase inhibition assay according to Choudary *et al*. (2011) [10]. 10 µL of 100 µg/mL extract was serially diluted with concentration variations of 50, 25, 12.5, 6.25, 3.125, 1.725, 0.613 µg/mL in DMSO, and then added with 10 µL of 10 mM pNPG substrate in phosphate buffer (pH 6.8), incubated at 37 °C for 5 minutes. Subsequently, 25 µL of α-glucosidase solution (0.05 U/mL in phosphate buffer containing 100 mg BSA) was added, and incubated for 30 minutes at 37 °C. The enzymatic reaction was stopped by adding 100 µL of 200 mM sodium carbonate, and absorbance was measured at a wavelength of 405 nm using a microplate reader (Biologix 800TS) [11].

Control experiments included blank (DMSO without extract) and acarbose with a concentration series of 100, 50, 25, 12.5, 6.25, 3.125, 1.725, and 0.613 µg/mL (positive control). For blank correction, sodium carbonate was added before the enzyme, followed by a second incubation. All tests were performed in triplicate. The inhibition percentage was calculated using the formula:

$$\text{Inhibition}\ (\%) = \left[\ 1 - \frac{A_{\text{sample}} - A_{\text{blank}}}{A_{blank}}\ \right] \times 100\% \quad \ldots\ldots (2)$$

A dose-response curve was constructed using GraphPad Prism v8.0 (Version 8.0), and the IC_{50} value was determined from sigmoidal regression analysis of the relationship between logarithmically transformed concentration and inhibition rate [11].

Separation of the ethyl acetate fraction of L. lavandulifolia leaves

The ethyl acetate fraction (5 g) was separated using gravity column chromatography with a silica gel stationary phase and an eluent of increasing polarity: *n*-hexane: ethyl acetate mixture (10:0 → 0:10). The separation results were analyzed by thin-layer chromatography (TLC), and fractions with identical TLC spot patterns were pooled to yield fractions F1–F8. Fraction F6 (0.1929 g) was subjected to re-chromatography using *n*-hexane: ethyl acetate (8:2) as the eluent. The separation results were again analyzed by TLC, yielding seven subfractions (F6.1–F6.7). Subfractions F6.3 and F6.5 exhibited the simplest spot patterns and were therefore selected for chemical composition analysis via GC-MS [12]

Chemical composition analysis using gas chromatography-mass spectrometry (GC-MS)

Chemical compound identification in the bioactive fraction was performed using an Agilent Technologies 7890B gas chromatograph coupled with a 5977B mass spectrometer (Agilent Technologies, USA), equipped with an HP-5MS UI capillary column (30 m × 0.25 mm × 0.25 µm). The sample (2 µL) was injected in split mode (12:1) with the injector temperature set at 350 °C. The oven temperature programmed commenced at 50 °C (hold 5 min), followed by a 10 °C/min ramp to 290 °C, and finally held at 290 °C for 15 min. Helium carrier gas was maintained at a constant flow rate of 1 mL/min. Electron ionization (EI) was operated at 70 eV, and mass spectra were acquired in scan mode across the *m/z* 50–300 range with a scan rate of 20 spectra/sec [12]. System control and data acquisition were managed using Agilent MassHunter Qualitative Navigator software (v.B.08.00).

RESULTS AND DISCUSSION

The leaf powder of *L. lavandulifolia* leaves (1000 g) was macerated with solvents of graded polarity (n-hexane, ethyl acetate, and methanol). After concentrating using a rotary evaporator, the concentrated fraction of n-hexane was 21.75 g (2.17%), the fraction of ethyl acetate was 49.54 g (4.95%), and the fraction of methanol was 49.22 g (4.92%).

α-Glucosidase Inhibition on the Fraction of L. lavandulifolia Leaves

The antidiabetic activity test of *L. lavandulifolia* leaf fractions through α-glucosidase Inhibition demonstrated increased percentage inhibition value with higher test concentrations. The ethyl acetate extract exhibited higher activity at the same concentration than the other extracts. The percentage inhibition values showed a linear relationship with activity. Based on these percentage inhibition values, the IC_{50} value could be determined via linear regression analysis (**Figure** 1). The IC_{50} value (**Table** 1) represents the concentration required to inhibit 50% of the enzyme activity.

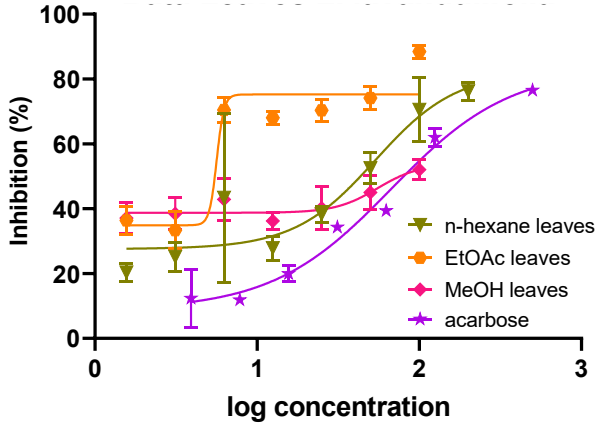

Figure 1. Graph of Inhibition of α-glucosidase activity fraction of *L. lavandulifolia* leaves

Table 1. IC_{50} values of the Inhibition of α-glucosidase activity

Sample	IC_{50}
n-Hexane fraction	53.58
Ethyl acetate fraction	5.634
Methanol fraction	55.3
Control (+) Acarbose	67.07

The ethyl acetate fraction yields a lower IC_{50} value than other fractions, with an IC_{50} of 5.634 µg/mL. Meanwhile, the positive control α-glucosidase inhibitor (acarbose) showed an IC_{50} of 67.07 µg/mL. These measurements indicate that the ethyl acetate fraction is more active than other fractions (*n*-hexane and methanol) and the positive control acarbose. The *n*-hexane and methanol fractions yield IC_{50} values of 53.58 µg/mL and 55.3 µg/mL, respectively. This data showed that the n-hexane and methanol fractions are more active in inhibiting α-glucosidase enzyme activity than the positive control (acarbose). The Butanol fraction of *S. polyanthum* (Wight) Walp was reported to show potent α-glucosidase inhibitory

activities with an IC_{50} of 28.469 ± 1.929 µg/ml, while the IC_{50} of acarbose was 111.286 ± 2.386 µg/ml [13].

Ethyl acetate is a semi-polar solvent that optimally extracts non-polar bioactive compounds (e.g., terpenoids, fatty acids) and semi-polar compounds (e.g., phenolic acids, flavonoids). These compounds bind competitively to the enzyme's active site or alter its conformational stability, thereby inhibiting the hydrolysis of the p-nitrophenyl glycoside substrate [14]. Phenolic compounds like gallic acid and flavonoids like quercetin, commonly found in ethyl acetate fractions, exhibit strong α-glucosidase inhibitory activity. Other chemical constituents, including acacetin, luteolin, and chrysoeriol, have been identified in *L. lavandulifolia* extracts [8,15].

Meanwhile, the methanol fraction exhibited lower activity compared to other fractions. This data can be explained by the tendency of the methanol fraction to attract polyphenolic compounds and glycosidic compounds. These compounds may sterically hinder enzyme-substrate interactions or form non-productive complexes with α-glucosidase, resulting in weaker inhibitory activity [16]. The lipophilic compounds can inhibit α-glucosidase through a non-competitive mechanism by binding to allosteric sites, as reported for *Nigella sativa* seed oil [17]. The chloroform extract of *L. lavandulifolia* has also been reported to possess antidiabetic activity [18]. These findings reinforce the ethnopharmacological use of *L. lavandulifolia* leaves in South Asia for diabetes treatment [19].

Separation of the Ethyl Acetate Fraction of L. lavandulifolia Leaves and Its Antidiabetic Activity

The ethyl acetate leaf fraction (5 g), after separation using gravity column chromatography and based on TLC patterns, yielded eight fractions F1–F8. Fraction F6 was identified as the potential fraction containing compounds that fluoresced under UV_{254nm} light, typically indicative of phenolic or flavonoid compounds, which are often active in α-glucosidase enzyme inhibition. Fraction F6 was then subjected to re-column chromatography, and TLC analysis yielded seven subfractions F6.1–F6.7 (**Table 2**).

Table 2. The separation of the ethyl acetate fraction from *L. lavandulifolia* Leaves

Fractions	Weight (mg)	Subfractions	Weight (mg)
F1	174.3	F6.1	30.3
F2	536.0	F6.2	17.9
F3	76.3	F6.3	14.8
F4	18.1	F6.4	17.3
F5	193.3	F6.5	16.2
F6	192.9	F6.6	31.3
F7	71.9	F6.7	51.3
F8	875.1	-	-

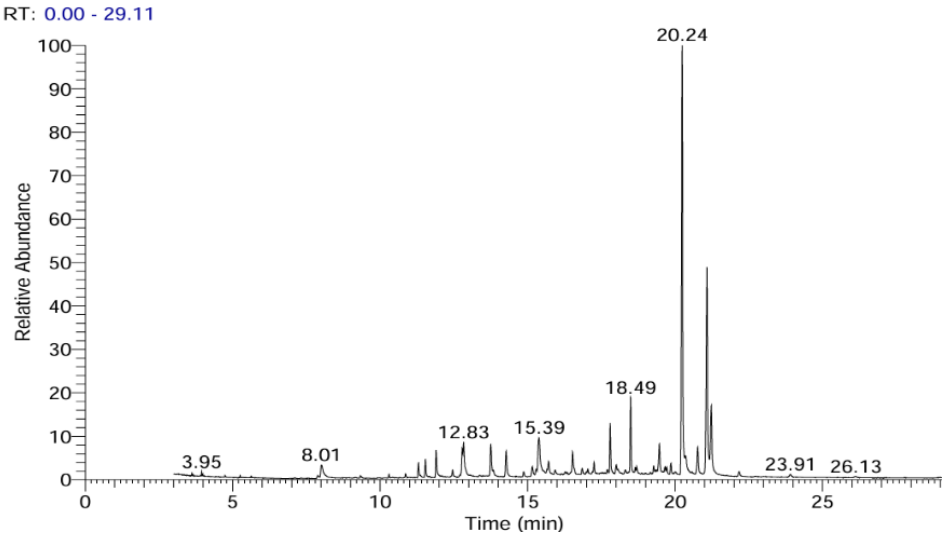

Figure 2. Chromatogram of GC-MS from subfraction F6.3 EtOAc leaves extract *L. lavandulifolia*

Table 3. Chemical compound identification of F6.3

No	Chemical Compounds	Formula Molecule	Rt (min)	Peak area (%)	Similarity index (%)
1	Hexadecanoic acid, methyl ester	$C_{17}H_{34}O_2$	12.83	5.51	83.3
2	1-Heneicosanol	$C_{21}H_{44}O$	13.75	3.44	88.4
3	10-Octadecenoic acid, methyl ester	$C_{19}H_{36}O_2$	15.39	6.48	84.6
4	1-Naphthalenepropanol, α-ethyldecahydro-4-hydroxy-α,2,5,5,8a-pentamethyl-,[1S-[1α(R*),2α,4α,4aα,8aα]]	$C_{20}H_{36}O_2$	17.80	3.11	74.5
5	Spiro[tetrahydrofuran-2,1'-decalin], 5-methyl-2'methylene-5',5',8a'-trimethyl-	$C_{18}H_{30}O$	18.49	4.89	74
6	1b,4a-Epoxy-2H-cyclopenta[3,4]cyclopropa[8,9]cycloundec[1,2-b]oxiren-5(6H)-one,7-(acetyloxy)decahydro-2,9,10a-trihydroxy-3,6,8,8,10a-pentamethyl-	$C_{28}H_{33}O_{11}$	19.47	2.94	71.9
7	Pthalic acid, di(2-prophylpentyl) ester	$C_{24}H_{38}O_4$	20.24	30.30	92.3
8	1-Naphthalenepropanol, α-ethenyldecahydro-4-hydroxy-α,5,5,8a-tetramethyl-2-methylene-,,[1S-[1α(R*),4α,4aα,8aα]]-	$C_{20}H_{34}O_2$	21.08	17.21	95.75

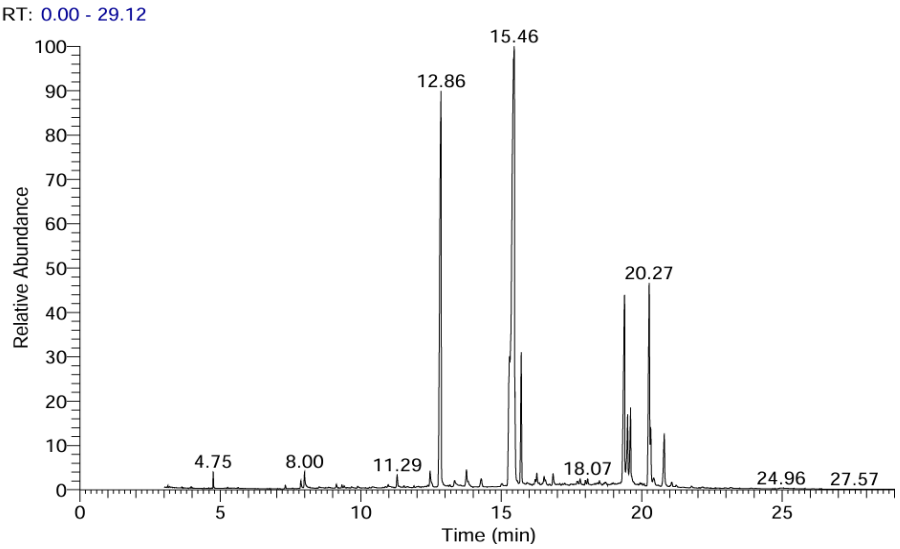

Figure 3. Chromatogram of GC-MS from F6.5 EtOAc leaves extract of *L. lavandulifolia*

Table 4. Chemical compound identification of F6.5

No	Chemical Compounds	Formula Molecule	RT (min)	Peak area (%)	Similarity index (%)
1	1-Hexadecanol, 2-methyl-	$C_{17}H_{36}O$	11.29	0.46	83.4
2	Hexadecanoic acid, methyl ester	$C_{17}H_{34}O_2$	12.85	19.91	95.9
3	10-Heneicosene (c,t)	$C_{21}H_{42}$	13.76	1.02	80.7
4	9-Octadecanoid acid (Z)-, methyl ester	$C_{19}H_{36}O_2$	15.46	45.38	96.2
5	Methyl stearate	$C_{19}H_{38}O_2$	15.71	3.84	94.7
6	Androstan-17-ol, 4,4-dimethyl-, (5α, 17α)-	$C_{19}H_{28}O_3$	19.38	8.02	74.3
7	Androstan-17-ol, 4,4-dimethyl-, (5α, 17α)-	$C_{19}H_{28}O_3$	19.60	2.54	75.4
8	Diisooctyl phthalate	$C_{24}H_{38}O_4$	20.27	9.21	91.1
9	2-Pentenoic acid, 5-(decahydro-5,5,8a-trimethyl-2-methylene-1-naphthalenyl)-3-methyl-,[1S-[1α(E),4aα,8aα]]-	$C_{20}H_{32}O_3$	20.80	2.24	70.5

Subfractions F6.3 and F6.5 exhibited distinct fluorescent spots. However, the subfraction quantities were minimal, so these fractions were analyzed via GC-MS. Subfraction F6.3 (**Figure** 2 and **Table** 3) revealed eight compounds, including fatty acid esters, long-chain alcohols, and 1-naphthalenepropanol. Fatty acid esters such as hexadecanoic acid methyl ester ($C_{17}H_{34}O_2$) with 5.51% abundance (Similarity Index, SI: 83.3%) and 10-octadecenoic acid methyl ester ($C_{19}H_{36}O_2$) with 6.48% abundance (SI: 84.6%) are postulated to contribute to glucosidase enzyme inhibition [20]. The highest abundance was shown by a naphthalene derivative (17.21% abundance, SI: 95.75%), which may also trigger Inhibition through enzyme conformational changes, thereby reducing substrate affinity [21].

Subfraction F6.5 (**Figure** 3 and **Table** 4) had fatty acid methyl esters as the dominant component with 65% abundance. The most dominant constituent was 9-octadecanoic acid (Z)-methyl ester (45.38%), structurally analogous to methyl oleate, inhibiting α-glucosidase through non-competitive binding to hydrophobic regions near the enzyme's active site, thereby disrupting substrate access and altering conformational stability [22]. Hexadecanoic acid methyl ester (19.91%) further enhanced Inhibition through Van der Waals interactions with surface residues [23].

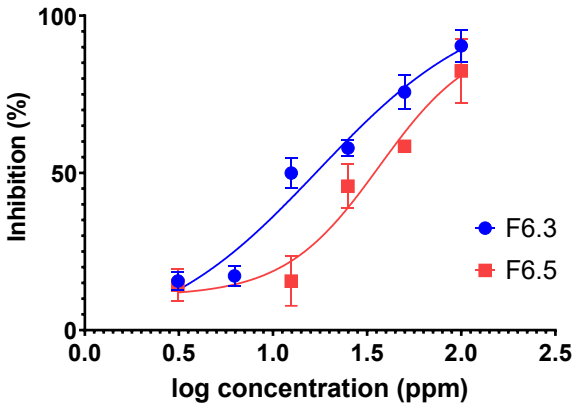

Figure 4. The Inhibition of α-glucosidase activity from subfraction F6.3 and F6.5

The α-glucosidase inhibitory activity of subfractions F6.3 and F6.5 yielded IC_{50} values of 17.3 and 36.72 µg/mL, respectively. This data indicates that subfraction F6.3 is more active than subfraction F6.5. Compared to the ethyl acetate fraction, the activities of subfractions F6.3 and F6.5 are weaker than that of the ethyl acetate fraction, indicating that in the fraction form, there is a synergy of chemical components in providing activity. A fraction is categorized as having strong activity if IC_{50} < 50 ppm [24]. Based on this category, the ethyl acetate fraction, subfraction F6.3, and subfraction F6.5 are strong activity categories. The different results were reported by Fauzia [25], where the Inhibitory concentration of the extract is higher than that of the fraction. The IC_{50} value of ethyl acetate extract was 37.39 µg/mL, while the methanol fraction was 60.01 µg/mL, the n-hexane fraction was 75.45 µg/mL, and acarbose was 124.39 µg/mL [25].

CONCLUSION

The ethyl acetate fraction of *Leucas lavandulifolia* leaves, as well as the column fraction, shows higher α-glucosidase inhibitory activity compared to the positive control acarbose and is classified in the strong category, with their main chemical content being fatty acid ester compounds and naphthalene derivatives.

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