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Antioxidant and Antidiabetic Activities of *Melastoma Malabathricum* Leaves Extracts

Muddatstsir Idris[1,2], Adi Setyo Purnomo[1], Fahimah Martak[1], Sri Fatmawati[1,3]*

[1] Department of Chemistry, Faculty of Science and Data Analytics, Institut Teknologi Sepuluh Nopember, Jalan Arif Rahman Hakim, Sukolilo, Surabaya 60111, East Java, Indonesia

[2] Program of Pharmacy Study, Faculty of Mathematics and Natural Sciences, University of Lambung, Mangkurat, A. Yani KM. 35.8 Banjarbaru 70714, South Kalimantan, Indonesia

[3] Agri-Food and Biotechnology Research Center, Institut Teknologi Sepuluh Nopember, Jalan Arif Rahman Hakim, Sukolilo, Surabaya 60111, East Java, Indonesia

Abstract: Currently, no effective medication is available to treat diabetes despite this disease is a serious health problem. As part of our project to explore Indonesian medicinal plants for antidiabetic agents, this study aimed to investigate the total phenolic and flavonoid contents, antioxidant and antidiabetic properties of *Melastoma malabathricum* leaves extracts. Spectrophotometric methods were used to determine the total phenolic and flavonoid contents. Antioxidant activity was performed using DPPH, ABTS, and FRAP methods. The *in vitro* antidiabetic test was conducted through an inhibitory evaluation of α-glucosidase and α-amylase, while STZ-induced diabetic rats were used for *in vivo* study. The highest value of total phenolic (183.71 ± 0.11 mg GAE/g Extract) was recorded in the methanolic extract and flavonoid (24.10 ± 0.04 mg QE/g Extract) contents were recorded in the EtOAc extract. The methanolic extract has the highest DPPH and ABTS activities with IC_{50} values of 8.58 ± 0.03 and 4.59 ± 0.03 μg/mL, respectively. It also showed the highest FRAP activity with a 51.15 ± 0.10 μM Fe^{2+}/g. *In vitro* antidiabetic testing of the methanolic extract of leaves against α-glucosidase and α-amylase was reported for the first time. This novel result showed that the methanolic extract inhibited α-glucosidase and α-amylase with IC_{50} values of 75.25±1.60 and 52.38±1.32 μg/mL, respectively. A dose of 200 mg/Kg body weight of the methanolic extract reduced rats' blood glucose rate and serum blood glucose by 51.01% and 37.82%, respectively, after 15 days of treatments. These findings suggested that the methanolic extract of *M. malabathricum* leaves can be used as a potential source of antioxidant and antidiabetic agents.

Keywords: antidiabetic activity, antioxidant, *Melastoma malabathricum*, *α*-glucosidase, *α*-amylase.

多花野牡丹叶提取物的抗氧化和抗糖尿病活性

摘要：糖尿病是一种危险的疾病，尽管糖尿病是一种严重的健康问题，但目前还不存在可用于治疗糖尿病的有效药物。作为我们探索印度尼西亚抗糖尿病药物药用植物项目的一部分，本研究的主要目的是为了调查*多花野牡丹叶*提取物的总酚类和类黄酮含量以及其抗氧化和抗糖尿病的性质。使用分光光度法测定总酚类和类黄酮含量。使用 DPPH，ABTS 和 FRAP 方法进行抗氧化活性。*体外*抗糖尿病试验通过α-葡萄糖苷酶和α淀粉酶的抑制性评价进行，而 STZ 诱导的糖尿病大鼠用于*体内*研究。在乙酸乙酯提取物中记录的总酚类（183.71±0.11 毫克盖伊/克提取物）的最高值，在乙酸乙酯提取物中记录了类黄酮（24.10±0.04 毫克量化宽松/克提取物）含量。甲醇提取物具有最高的 DPPH 和 ABTS 活性，我知道了 $_{50}$ 值分别为 8.58±0.03 和 4.59±0.03 微克/毫升。它还显示出最高的 FRAP 活性，值为 51.15±0.10μ

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About the authors: Muddatstsir Idris, Department of Chemistry, Faculty of Science and Data Analytics, Institut Teknologi Sepuluh Nopember, Surabaya, Indonesia; Program of Pharmacy Study, Faculty of Mathematics and Natural Sciences, University of Lambung, Banjarbaru, Indonesia; Adi Setyo Purnomo, Fahimah Martak, Department of Chemistry, Faculty of Science and Data Analytics, Institut Teknologi Sepuluh Nopember, Surabaya, Indonesia; Sri Fatmawati, Department of Chemistry, Faculty of Science and Data Analytics, Institut Teknologi Sepuluh Nopember, Surabaya, Indonesia; Agri-Food and Biotechnology Research Center, Institut Teknologi Sepuluh Nopember, Surabaya, Indonesia

Corresponding author Sri Fatmawati, fatma@chem.its.ac.id

金属铁 $^{2+}$/g。此叶的甲醇提取物针对*α*淀粉酶和*α*葡萄糖苷酶的*体外*抗糖尿病实验被初次报道。这个新的结果表示甲醇提取物抑制了*α*淀粉酶和*α*葡萄糖苷酶，以我知道了 $_{50}$ 值分别为 75.25±1.60 和 52.38±1.32 微克/毫升。甲醇提取物的剂量为 200 毫克/公斤体重，在 15 天治疗后将大鼠的血糖率和血清血糖分别降低了 51.01%和 37，82%。这些发现表明，多花野牡丹叶的甲醇提取物可用作抗氧化剂和抗糖尿病药物的潜在来源。

关键词：抗糖尿病活性， 抗氧化剂， 多花野牡丹， α葡萄糖苷酶，α淀粉酶.

1. Introduction

Type 2 diabetes mellitus (DM) is the main type of DM, accounting for more than 90% of cases [1]. It is caused by pancreatic cell dysfunction and insulin resistance in target organs resulting from impaired homeostasis [2]. Furthermore, type 2 diabetes causes foot ulcers, diabetic retinopathy, nephropathy, stroke, cardiovascular diseases, and neuropathy [1]. α-amylase catalyzes the first step in the breakdown of starch by hydrolyzing the polysaccharide (starch) into three primary products, namely maltose, maltotriose, and limited dextrins, while α- glucosidase catalyzes the end step in the digestion of starch and disaccharides [3]. Due to insensitivity or lack of insulin, the body's cells cannot properly metabolize sugar as diabetes develops. This occurs when the pancreas does not produce enough insulin for the effective use of the body [4]. Therefore, an effective therapeutic approach to controlling blood glucose levels is to inhibit or suppress the activity of Carbohydrate hydrolysis enzymes such as alpha-amylase and alpha-glucosidase. Additionally, traditional medicinal plant therapy can slow down glucose absorption into the blood by inhibiting α-glucosidase [1] and α-amylase enzymes [3].

Melastoma malabathricum L. is a plant species from the Melastomataceae family commonly distributed in South Kalimantan, Indonesia. Its roots, bark, and leaves are used as medicine to treat leucorrhoea, hemorrhoids, diarrhea, wounds, dysentery, stomachache, confinement infections, toothache, thrush, flatulence, and sore legs in Indonesian, Malay, and Indian [5]. Furthermore, the bioactivities of the Melastomataceae family include antinociceptive, antibacterial, antifungal, antiparasitic, antioxidant, anticoagulant, anti-ulcer, anti-diarrheal, antipyretic [6], cytotoxic [7], and anti-inflammatory properties [8].

The bioactive constituents reported from the *M. malabathricum* include tannins, flavonoids, phenolics, and glycosides. Furthermore, the methanol extracts of the flower of this plant showed DPPH radical scavenging activity with an IC_{50} value of 17.23 µg/ml [6]. Meanwhile, there are no reports on α-glucosidase and α-amylase inhibitory activity of *M. malabathricum* extracts. The chemical compounds isolated from this plant are linoleic acid 2,3-bis-(O-TMS)-propyl ester, *β*-amyrin, α-linolenic acid, *β*-sitosterol, palmitic acid [6], and kaempferol-3-O-(2′,6′-di-O-trans-p-coumaroyl)-*β*-D glucopyranoside [9].

However, there is a limited comprehensive study regarding the antidiabetic and antioxidant evaluation of the *M. malabathricum* leaves extract. Therefore, this study was conducted to evaluate Total Phenolic Content (TPC) and Total Flavonoid Content (TFC), antioxidant activities (DPPH, ABTS, and FRAP), and antidiabetic activities *in vitro* and *in vivo* of leaves extracts of *M. malabathricum.*

2. Materials

2.1. Plant Material

The leaves of *M. malabathricum* were collected in June 2019 at Banjarbaru, South Kalimantan, Indonesia, and identified by Mr. Edi, a botanist at Purwodadi Botanical Garden, Pasuruan, Indonesia. The voucher specimen was deposited at Laboratory of Natural Science and Synthetic Chemistry, Institut Teknologi Sepuluh Nopember, Surabaya, Indonesia (013/VI/HT-KIBAS/2019).

2.2. Extract Preparation

A total of 20 g of dried leaves of *M. malabathricum* were extracted with 250 ml of *n*-hexane, dichloromethane (CH_2Cl_2), and ethyl acetate (EtOAc), while 3.6 Kg of dried leaves of *M. malabathricum* were extracted with 41 L of methanol (MeOH) for 24 hours. The extract was filtered using filter paper and concentrated with a rotary evaporator to give a dry extract.

2.3. Animals

Male albino Wistar rats (160-200 g) used were given a standard pellet diet and placed in cages at a relative humidity of 55±10% and temperature of 25±1^{o}C. The experimental protocol was approved by the Health Research Ethics Committee of the School of Medicine, Airlangga University (161/EC/KEPK/FKUA/2021).

3. Methods

3.1. Total Phenolic Content (TPC)

The TPC of the MeOH, EtOAc, CH_2Cl_2, and *n*-hexane extracts of *M. malabathricum* was determined using Follin–Ciocalteu's method [10]. First, extracts with various concentrations in methanol were taken at 0.5 mL and mixed with 2.5 mL of 10% Follin–Ciocalteu's reagent from Sigma-Aldrich (St. Louis, MO, USA) and 2.0 mL of 7.5% sodium carbonate solution. Absorbance was measured using a UV-Vis spectrophotometer at 765 nm after incubating the mixture at 40◦C for 1 h. Next, Gallic acid (Sigma-Aldrich) with a concentration of 0 to 200 mg/L was used as the standard curve. The TPCs of the extracts were calculated as mg GAE (gallic acid equivalent)/g of dry extract.

3.2. Total Flavonoid Content (TFC)

The TFC of the MeOH, EtOAc, CH_2Cl_2 and *n*-hexane extracts of *Melastoma malabathricum* leaves was measured by spectrophotometer, as previously reported method [11] with minor modification. The evaluation was performed by mixing 0.5 mL of each extract (100–1000 ppm) with 0.5 mL of 2% $AlCl_3$ (Sigma-Aldrich) solution in MeOH. The mixture was incubated for 1 hour, and the absorbance was measured at 415 nm using a spectrophotometer. Quercetin (Sigma-Aldrich) with a concentration of 0 to 50 mg/L was used as the standard curve. The TFCs of the extracts were calculated as mg QE (quercetin equivalent)/g of dry extract.

3.3. DPPH Radical Scavenging Assay

The antioxidant activity was determined using DPPH (1,1-diphenyl-2-picrylhydrazyl), as previously stated [12]. During the process, 33.3 µL of the extract at different concentrations (159.73 - 4.99 µg/mL) was added to 1 mL of DPPH 6.0×10^{-5} M. The mixture was incubated for 20 minutes in a dark room at 37°C. Subsequently, the absorbance was measured using UV-Visible Spectrophotometer at 517 nm (Thermo Fisher Scientific, USA) with three replications. The blank sample was a mixture of 33.3 µL of DPPH and methanol solution, while gallic acid was used as the positive control. The DPPH radical scavenging assay percentage was calculated by applying the following equation.

$$Inhibition\ (\%) = \frac{(Blank\ abs - sample\ abs)}{Blank\ abs} x\ 100\% \quad (1)$$

3.4. ABTS Radical Scavenging Assay

ABTS, 2,2"-azino-bis (3-ethylbenzothiazoline-6-sulfonic acid) radical scavenging assay was performed using the method [13]. The evaluation was performed by mixing 5.0 mL of 7 mM ABTS stock solution with 88 µL of 140 mM potassium peroxydisulfate ($K_2S_2O_6$) and stored in the dark at room temperature for 12–16 h before usage. The mixture was mixed with a 99.5 % ethanol solution until a working solution was obtained with an absorbance of 0.7 (±0.02) at 734 nm. Each extract with various concentrations (49.51 – 1.55 µg/mL) was added to 1 mL of the working solution and then stirred manually for 10 s and incubated for 4 min at 30°C. The absorbance of each solution was measured at 734 nm with a UV-Vis spectrophotometer. Gallic acid and ethanol were used as a positive control and blank sample, respectively. The ABTS radical scavenging assay was calculated with equation 1.

3.5. Ferric-Reducing Antioxidant Power (FRAP) Assay

The FRAP assay was determined using the method stated by [14] with slight modification. The reduction of colorless Fe^{3+}-tripyridyltriazine to strongly blue-colored Fe^{2+}-tripyridyltriazine is often evaluated by measuring the absorbance change at 593 nm. Ten mM of 2,4,6-Tris(2-pyridyl)-s-triazine (TPTZ) (Sigma-Aldrich) solution in 40 mM HCl, 300 mM acetate buffer pH 3.6, and 20 mM $FeCl_3 \cdot 6H_2O$ were mixed in the ratio of 1:10:1 to get working FRAP reagent. $FeSO_4 \cdot 7H_2O$ used for FRAP standard curve. Sample solution (100 µL), distilled water (900 µL), and FRAP reagent (2 mL) were mixed and incubated at 37 ◦C in a dark room for 30 min. The mixture absorbance was measured at 593 nm using UV-Visible Spectrophotometer. A mixture of FRAP reagent (2 mL) and H_2O (1 mL) was used as the blank sample. The FRAP values were stated as mM Fe^{2+}/g of sample ((FRAP value of sample (µM) = abs (sample) × FRAP value of std (µM)/abs (std)).

3.6. *In Vitro* α-Glucosidase Inhibitory Activity

The anti-α-glucosidase assay was performed using rat intestinal enzyme [15]. The rat enzyme solution was prepared from rat intestinal acetone powder (Sigma, St. Louis). 1 g of rat intestinal acetone powder was homogenized in 30 mL of normal saline. After centrifugation (12,000 g × 30 min), the aliquot was subjected to assay. First, 10 µL of the extracts of *M. malabathricum* leaves (5 mg/mL in DMSO) were added with 50 µL of the 0.1 M phosphate buffer (pH 6.9), 20 µL of the maltose substrate solution (10 mM) in 0.1 M phosphate buffer, 80 µL of glucose assay kit (SU-GLLQ2, Human), and 20 µL of the rat enzyme solution. The reaction mixture was then incubated at 37°C for 10 min. A microplate reader (BioTek ELx800TM, BioTek Instruments, Inc, Winooski, VT, USA) was used to measure the absorbance of enzymatic activity at 520 nm. Inhibition (%) was calculated based on equation 2.

$$Inhibition\ (\%) = \frac{(Blank\ abs - sample\ abs)}{Blank\ abs} x\ 100\% \quad (2)$$

where $Abs_{blank} = Abs_{\text{enzyme reaction}} - Abs_{\text{blank of enzyme reaction}}$, $Abs_{sample} = Abs_{\text{sample reaction}} - Abs_{\text{blank of sample reaction}}$.

3.7. *In Vitro* α-Amylase Inhibitory Activity

The anti-α-amylase assay was adapted from [16] with a slight modification. First, 10 mg of the sample was dissolved in 1 mL of DMSO. Next, the α-amylase enzyme was prepared by dissolving the porcine pancreas α-amylase (5 mg) in 1 mL of 0.1 M phosphate buffer (pH 6.9). Then, 100 mg of starch potato (substrate) was warmed in 5 mL of 0.1 M phosphate buffer (pH 6.9) for 5 minutes and cooled at room temperature. After that, a sample (10 µL) and substrate (250 µL) were mixed into 150 µL of 0.1 M phosphate buffer (pH 6.9). After preincubation for 5 minutes, 100 µL α-amylase enzyme was added to the mixture and further incubated at 37°C for 15 minutes. The reaction was stopped by adding 1M HCl (250 µL) and 10% iodine solution (250 µL). Acarbose was used as a positive control, and the absorbance was measured at 650 nm by a microplate reader (BioTek ELx800TM, BioTek Instruments, Inc, Winooski, VT, USA). The inhibition percentage was calculated using equation 2.

3.8. *In Vivo* Antidiabetic Activity Assay

The *in vivo* antidiabetic assay was slightly modified from [17]. The male albino Wistar rats fasted 8-12 hours before streptozocin (STZ) injection. Furthermore, they were induced by STZ (60 mg/Kg) using a single intraperitoneal injection. The blood glucose rate was observed on the third day after STZ injection. Afterward, rats with blood sugar rates above 200 mg/dL were used for further testing. Diabetic rats were divided into five groups as follows: G-1 (0.5% of NaCMC as negative control), G-2 (10 mg/Kg of glibenclamide as positive control), G-3 (200 mg/Kg of extract), G-4 (400 mg/Kg of extract), and G-5 (600 mg/Kg of extract). Additionally, one group is used for normal control (without treatment), named G-6. One group consists of four rats. The NaCMC, glibenclamide, and extract were administered orally for 15 days. Blood glucose was measured at 0, 3, 6, 9, 12, and 15 days by ACCU Check Instant, and the serum glucose was measured at 0 and 15 days using a spectrophotometer UV-Vis. Serum glucose analysis was performed using the glucose test method. First, 1 mL of rat blood was transferred to a centrifuge tube and centrifuged at 4000 rpm for 15 minutes to separate the blood plasma and serum. The serum (10 µL) was mixed with 1000 µL of kit reagent, then put into a test tube and vortexed to make it homogeneous. The mixture was incubated at 37 ^{o}C for 10 minutes, while the absorbance was measured at 500 nm. The absorbance measurement of the blank and standard (glucose) was conducted the same way as the sample, and the serum glucose (mg/dL) was calculated using equation 3:

$$Glucose\ \left(\frac{mg}{dL}\right) = \frac{Sample\ abs}{Standard\ abs} x\ Glucose\ standard\ \left(\frac{mg}{dL}\right) \quad (3)$$

3.9. Statistical Analysis

The data were summarized using the formula of mean ± standard deviation. A linear regression equation was used to determine concentrations of antioxidants. Concentrations of anti-α-glucosidase and anti-α-amylase activities were determined using a non-linear regression equation. The results of *in vivo* antidiabetic assays were analyzed by ANOVA followed by Least Significance Different (LSD) if there was a significant difference. P-value < 0.05 was considered statistically significant.

4. Results

4.1. Total Phenolic and Flavonoid Contents

Table 1 shows the TPC and TFC values of *n*-hexane, CH_2Cl_2, EtOAc, and MeOH extracts from the *M. malabathricum* leaves. Methanol extract has the highest TPC with a value of 183.71 ± 0.11 (mg GAE/g Extract), while EtOAc extract showed the highest TFC with a value of 24.10 ± 0.04 (mg QE/g Extract).

Table 1 TPC and TFC values of *M. malabathricum* leaves extracts

Extracts	TPC (mg GAE/g Extract)	TFC (mg QE/g Extract)
n-Hexane	26,97 ± 0.19	16.77 ± 0.05
CH_2Cl_2	27,21 ± 0.17	22.69 ± 0.04
EtOAc	78,87 ± 0.14	24.10 ± 0.04
MeOH	183.71 ± 0.11	23.18 ± 0.05

Note: Data are expressed as mean ± SD of triplicate experiments.

4.2. Antioxidant Activity

Table 2 shows the antioxidant properties of *n*-hexane, CH_2Cl_2, EtOAc, and MeOH extracts from the leaves of *M. malabathricum*. Methanol extract has the best activity compared to other extracts for DPPH and ABTS tests, with IC_{50} values of 8.58 ± 0.03 and 4.59 ± 0.03 (µg/mL). For FRAP assay, methanol extract has the highest value compared to other extracts, with a value of 51.15 ± 0.10 (µM Fe^{2+}/g).

Table 2 The results of *in vitro* antioxidant test of *M. malabathricum* leaves extracts

Extracts	DPPH	ABTS	FRAP (µM Fe^{2+}/g)
	IC_{50} (µg/mL)	IC_{50} (µg/mL)	
n-Hexane	51,92 ± 0,12	28.23 ± 0.04	12.08 ± 1.10
CH_2Cl_2	48.26 ± 0.16	25.12 ± 0.02	32.96 ± 0,17
EtOAc	37.35 ± 0.07	12.78 ± 0.04	38.75 ± 2.41
Methanol	8.58 ± 0.03	4.59 ± 0.03	51,15 ± 0.10
Gallic acid	5.29 ± 0.02	0.12 ± 0.01	Nt
Ascorbic acid	Nt	Nt	30.62 ± 0.27

Note: Data are expressed as mean ± SD of triplicate experiments, Nt: not tested

4.3. *In Vitro* Antidiabetic Assay

The antidiabetic activity of the extract was tested using the α-glucosidase and α-amylase enzyme inhibition method. Table 3 shows the results of *in vitro* antidiabetic assay. The screening result of anti-α-glucosidase showed that the methanol extract had the best anti-α-glucosidase activity compared to the other extracts and thus was used for in vivo study.

Table 3 The *in vitro* antidiabetic activity of *M. malabathricum* leaves extracts

	α-Glucosidase		**α-Amylase**	
Extracts	% Inhibition ± SD (5 mg/mL)	IC_{50} (µg/mL)	% Inhibition ± SD (5 mg/mL)	IC_{50} (µg/mL
n- hexane	3.46 ± 4.10	Nt	Nt	Nt
CH_2Cl_2	5.54 ± 0.51	Nt	Nt	Nt
EtOAc	44.95 ± 0.20	Nt	Nt	Nt
Methanol extract	73.74 ± 1.60	75.25 ± 1.60	77.62 ± 2.21	52.38 ± 1.32
Acarbose	87.14 ± 2.36	7.67 ± 1.14	94.01 ± 1.56	8.70 ± 0.79

Note: Data are expressed as mean ± SD of triplicate experiments, Nt - not tested

4.4. *In Vivo* Antidiabetic Assay

4.4.1. Effect of M. Malabathricum Extract on Rat Blood Glucose

Table 4 shows the effect of methanol extract of *M. malabathricum* leaves on rat blood glucose levels during 15 days of treatment. The results showed that a dose of 200 mg/Kg of the extract reduced the blood glucose level by 51.01%, while doses of 400 and 600 mg/Kg were reduced by 9.50% and 10.42%, respectively.

Table 4 Effect of *M. malabathricum* extract on blood glucose level in diabetic rats

Treatment Groups	**Blood glucose level (mg/dL) on day**						**Blood glucose loss (%)**
	0	**3**	**6**	**9**	**12**	**15**	
Negative control (G-1)	559.50 ± 28.20	428.50 ± 55.67	416.75 ± 54.41	458.25 ± 41.04	443.25 ± 54.39	556.50 ± 26.50	0.53 ± 0.41
Positive control (G-2)	475.75 ± 60.72	466.00 ± 116.20	402.25 ± 62.14	377.50 ± 63.40	409.25 ± 53.27	340.00 ± 35.59	28.53 ± 5.01
Dose I (200 mg/Kg) (G-3	537.50 ± 75.00	478.75 ± 59.07	358.25 ± 63.80	295.25 ± 68.68	290.00 ± 69.73	272.25 ± 46.35	51.01 ± 11.12
Dose II (400 mg/Kg) (G-4)	459.30 ± 35.26	400.80 ± 33.08	351.30 ± 58.31	297.30 ± 29.97	373.80 ± 47.93	415.50 ± 29.80	9.50 ± 0.58
Dose III (600 mg/Kg) (G-5)	492.25 ± 13.40	497.00 ± 68.09	416.75 ± 54.41	400.25 ± 30.59	414.25 ± 19.47	441.00 ± 18.87	10.42 ± 2.48
Normal control (G-6)	109.5 ± 5.10	97.50 ± 14.06	97.50 ± 14.06	100.50 ± 6.86	109.25 ± 6.88	109.25 ± 5.62	0.00 ± 0.00

Note: Values are means ± SD (n = 4), significantly different from normal control ($p < 0.05$)

4.4.2. Effect of M. Malabathricum Extract on Rat Body Weight

Table 5 shows the effect of methanol extract from *M. malabathricum* leaves on rat body weight. The test results showed that the body weight of rats given the extract at a dose of 400 and 600 mg/Kg decreased by 4.00% and 13.05%, respectively, while a dose of 200 mg/Kg increased the body weight of rats by 6.92%.

Table 5 Effect of *M. malabathricum* extract on body weights in diabetic rats

Treatment Groups	**Beginning**	**The rat's body weight (g) on day**						**Blood glucose loss (%)**
		0	**3**	**6**	**9**	**12**	**15**	
Normal control	158.00 ± 6.06	158.50 ± 6.35	159.25 ± 6.18	159.75 ± 5.44	158.50 ± 5.45	158.50 ± 3.70	156.75 ± 4.99	↓0.79 ± 0.59
Negative control	215.25 ± 15.69	200.75 ± 24.60	201.25 ± 27.97	196.50 ± 28.01	195.0 ± 26.52	192.75 ± 29.84	174.25 ± 10.36	↓19.05 ± 1.35
Positive control	166.25 ± 6.55	161.75 ± 7.89	160.50 ± 6.61	158.25 ± 3.50	157.75 ± 4.72	155.50 ± 4.73	153.50 ± 5.00	↓7.67 ± 1.45
Dose I (200 mg/Kg)	173.50 ± 1.91	168.00 ± 4.69	170.50 ± 6.76	172.25 ± 5.74	176.25 ± 4.65	175.75 ± 4.03	185.50 ± 1.29	↑6.92 ± 0.88
Dose II (400 mg/Kg)	158.00 ± 8.25	145.25 ± 10.08	150.00 ± 14.67	143.50 ± 10.85	148.00 ± 17.34	147.75 ± 18.45	151.75 ± 9.60	↓4.00 ± 1.14
Dose III (600 mg/Kg)	170.25 ± 3.40	161.75 ± 2.63	160.50 ± 5.26	158.75 ± 5.12	156.50 ± 6.81	155.50 ± 8.96	147.25 ± 3.30	↓13.50 ± 1.83

Note: Values are means ± SD (n = 4), significantly different from normal control ($p < 0.05$), ↓ = decrease, ↑ = increase

4.4.3. Serum Blood Glucose

According to the analysis shown in Table 6, a 200 mg/Kg dose decreased the serum glucose levels in rats by 37.82%, from 5.95 mg/dL to 3.70 mg/dL.

Table 6 Serum blood glucose of rats treated with *M. malabathricum* extract

Treatment groups	**Serum glucose (mg/dL) on day**	
	0	**15**
Normal control	1.39 ± 0.19	1.40 ± 0.19
Negative control	3.14 ± 0.60	4.76 ± 1.02
Positive control	5.34 ± 1.33	5.43 ± 1.46
Dose I (200 mg/Kg)	5.95 ± 0.29	3.70 ± 0.34
Dose II (400 mg/Kg)	3.61 ± 0.18	3.83 ± 0.12
Dose III (600 mg/Kg)	4.47 ± 0.81	5.68 ± 0.16

Note: Values are expressed by means ± SD (n = 4), significantly different from normal control ($p < 0.05$)

4.5. Correlation of TPC, TFC, and Antioxidants

Table 7 shows the Pearson correlation coefficient of TPC, TFC, and antioxidant activities of *M. malabathricum* leaf extracts.

Table 7 Pearson correlation coefficient of total phenolic, total flavonoids, and antioxidants activities

	TPC[a]	**TFC[b]**	**DPPH[c]**	**ABTS[c]**	**FRAP[c]**
TPC	1				
TFC	0.488*	1			
DPPH	0.03*	0.471*	1		
ABTS	0.053*	0.309*	0.945*	1	
FRAP	0.828*	0.883*	0.141*	0.094*	1

* Correlation is significant at the 0.05 level

[a] Total phenolics content

[b] Total flavonoids content

[c] Coefficient of antioxidant

5. Discussion

5.1. Total Phenolic and Flavonoid Contents

The TPC values of the *M. malabathricum* extracts were determined from a linear gallic acid standard curve. Table 1 shows that the MeOH extract had the highest TPC value, followed by the EtOAc and CH_2Cl_2 extracts. This implies that the phenolic compounds in the leaves of this plant are mostly polar and semi-polar. Meanwhile, the TFCs of the *M. malabathricum* extracts

were determined from a linear quercetin standard curve. Table 1 shows that the EtOAc had the highest TFC value, followed by the MeOH and CH_2Cl_2 extracts. Finally, flavonoid compounds were accumulated in polar solvents and lower in nonpolar solvents [18].

5.2. Antioxidant Assay

The antioxidant assay was conducted using the *in vitro* DPPH radical scavenging method to evaluate the free radical scavenging activity of several natural product extracts [19]. Table 2 shows the DPPH radical scavenging assay conducted on *n*-hexane, CH_2Cl_2, EtOAc, and methanol extracts of *M. malabathricum* leaves and gallic acid (positive control) with IC_{50} values of 51.92 ± 0.12, 48.26 ± 0.16, 37.35 ± 0.07, 8.58 ± 0.03, and 5.29 ± 0.02, respectively. The result indicated that the methanol extract showed the highest antioxidant activity compared to the less polar extracts and was comparable to the positive control due to abundant phenolic constituents in the polar part. Furthermore, it complies with the results of the phenolic content of methanol extract analysis, which is higher than less polar extracts (Table 1). The methanol extract from *M. malabathricum* flowers showed antioxidant (DPPH) activity with an IC_{50} value of 17.23 μg/mL [6]. The research results were higher regarding the possibility of using different extracts than those reported by [6].

Table 2 shows that the highest ABTS assay results were observed in methanol extract with an IC_{50} value of 4.59 ± 0.03, followed by EtOAc extract with an IC_{50} value of 12.78 ± 0.04. The EtOAc and MeOH extracts showed better activity in the ABTS test than in the DPPH test, with possible differences in the reactions of phenolic compounds and free radicals in the organic and aqueous phases of the DPPH and ABTS assay [12].

The FRAP assay of Table 2 shows that methanol extract has the highest value, approximately two times that of ascorbic acid as a positive control, with a value of 51,15 ± 0.10 (μM Fe^{2+}/g), followed by EtOAc and CH_2Cl_2 with values of 38.75 ± 2.41. and 32.96 ± 0.17 (μM Fe^{2+}/g), respectively. The evaluation shows a sample capacity to participate in a one-electron redox reaction [20]. FRAP is directly proportional to the TPC and TFC values due to the presence of phenolic compounds and flavonoids, which act as electron donors to neutralize free radicals.

This study correlates antioxidant activities, TFC, and TPC of *M. malabathricum* leaves extracts. Pearson correlation was used to determine the relationship. A moderate correlation was observed between TPC and TFC with r = 0.488 ($p < 0.05$). A weak correlation was observed between DPPH and TPC with r = 0.03 ($p < 0.05$), but DPPH had a moderate correlation with TFC (r = 0.471, $p < 0.05$). ABTS vs TPC showed a weak correlation with r = 0.053 ($p < 0.05$), but ABTS had a moderate correlation with TFC (r = 0.309, $p < 0.05$). A strong correlation was observed between ABTS and DPPH with r= 0.945 ($p<0.05$). FRAP vs TPC and FRAP vs TFC showed a strong correlation with r = 0.828 ($p < 0.05$) and r = 0.883 ($p < 0.05$), respectively. A positive correlation was observed between FRAP and DPPH with r = 0.141 ($p < 0.05$). FRAP had a weak correlation with ABTS (r = 0.094, $p < 0.05$). Generally, TPC and TFC play an important role in antioxidant activity, acting as electron donors, chain breakers, and free radical scavengers [21]. This data showed a positive correlation between TPC and TFC with antioxidant activities.

5.3. *In Vitro* Antidiabetic Assay

Table 3 showed that the results of the anti-α-glucosidase assay of methanol extract and acarbose as a positive control at 5 mg/mL were 73.74 ± 1.60% and 87.14 ± 2.36%, respectively. In addition, the IC_{50} of the anti-α-glucosidase activity test was performed on the methanol extracts. Table 3 showed that the anti-α-glucosidase (IC_{50}) of *M. malabathricum* leaves methanol extract and acarbose as a positive control were 75.25 ± 1.60 and 7.67 ± 1.14 μg/mL, respectively. These results provided a reference for further studies on the benefits of using *M. malabathricum* leaves extracts as antidiabetic drugs because there are no previous reports on *in vitro* α-glucosidase inhibition tests from the methanol extract of the leaves. The inhibition of α-glucosidase is one of the therapies for treating type 2 diabetes mellitus.

Furthermore, this enzyme is commonly discovered at the border of the small intestine. Sugar production is inhibited by α-glucosidase inhibitors, which delay the absorption of complex carbohydrates. As a result, it gradually reduces glucose absorption, lowering blood sugar levels [1].

Table 3 showed that the anti-α-amylase assay of methanol extract and acarbose as a positive control at 5 mg/mL were 77.62 ± 2.21 and 94.01 ± 1.56%, respectively. It also showed that the IC_{50} of anti-α-amylase of the extract and acarbose were 52.38 ± 1.32 and 8.70 ± 0.79 μg/mL, respectively. This result indicated that the extract could be used as an inhibitor of the α-amylase enzyme. Meanwhile, an effective way to manage diabetes mellitus is to reduce postprandial hyperglycemia by slowing glucose absorption. This is obtained when the α-amylase activities in hydrolyzing carbohydrates can be inhibited in the digestive organs [3].

5.4. *In Vivo* Antidiabetic Assay

5.4.1. Effect of M. Malabathricum Extract on Rat Blood Glucose

Table 4 showed that STZ increases rats' blood glucose levels after the injection since the result obtained was more than 200 mg/dL. Furthermore, it

causes a diabetogenic effect, characterized by selective destruction of pancreatic islet *β*-cells, causing animals to exhibit insulin deficiency, hyperglycemia, polydipsia, and polyuria [22].

Table 4 shows the decrease in the blood glucose of rats administered methanol extract from *M. malabathricum* leaves. The result showed that normal control had no changes in blood glucose levels, while negative control decreased by 0.53%. The positive control can reduce the glucose levels by 28.53%, which implies that glibenclamide at a 10 mg/Kg dose can lower rats' blood glucose. Furthermore, the 200 mg/Kg dose showed the highest reduction in blood glucose (51.01%) of the other two doses. This finding revealed that the extract could protect and repair β-cells at an optimal 200 mg/Kg dose. Meanwhile, 400 and 600 mg/Kg doses lower the blood glucose levels by only 9.50 and 10.42%, respectively. Furthermore, this showed that doses above 200 mg/Kg indicate a downward trend in protecting and repairing *β*-cells, inhibiting insulin production. The blood glucose levels in diabetic rats decreased significantly ($p < 0.05$) with the administration of *M. malabathricum* leaves methanol extract. These results were significantly different from the normal group based on the ANOVA and LSD analysis results.

Plants have antihyperglycemic activity because they can restore pancreatic tissue function, increase insulin production, inhibit intestinal glucose absorption, and facilitate metabolites in insulin-dependent processes [23].

5.4.2. Effect of M. Malabathricum Extract on Rat Body Weight

Table 5 shows the effect of *M. malabathricum* leaves methanol extract on the rats' body weight. The normal control had a slight change in body weight. Meanwhile, the weight loss percentage from negative, positive control doses of 400 mg/Kg and 600 mg/Kg was 19.05, 7.67, 4.00, and 13.50%, respectively. This result was relatively high in the negative control and a 600 mg/Kg dose. The negative control was only given NaCMC, which did not reduce blood glucose levels but affected weight loss. The increased blood glucose levels in people with diabetes are generally accompanied by weight loss, polyuria, polydipsia, and polyphagia.

Meanwhile, the weight loss may be due to impaired fat and protein catabolism [23]. The weight loss percentage from the positive control was smaller than the negative control and the 600 mg/Kg dose treatment, demonstrating a better effect on lowering blood glucose than the two doses. Additionally, the treatment using 200 mg/Kg doses increased body weight. This implies that the dose protects the protein structure degradation [23]. Finally, the body weight of diabetic rats changed significantly ($p < 0.05$) on the administration of *M. malabathricum* leaves methanol extract. These results were significantly different from the normal group based on the ANOVA and LSD analysis results.

5.4.3. Serum Blood Glucose

The results of the analysis of serum glucose levels are shown in Table 6. The normal controls did not experience changes in serum glucose levels. Meanwhile, negative and positive controls and doses of 400 and 600 mg/Kg experienced an increased serum blood glucose level. It indicates that these treatments did not have the effect of reducing serum glucose levels in the rats. However, a 200 mg/Kg dose can reduce serum glucose levels in rats which is in line with decreasing blood glucose rates in plasma and serum.

The analysis showed that when *M. malabathricum* extract was administered at a 200 mg/Kg dose, serum blood glucose tended to decrease glucose rates. Additionally, the serum blood glucose of diabetic rats decreased significantly ($p < 0.05$) with the administration of the methanol extract. These results significantly differed from the normal group based on the ANOVA and LSD analysis results.

6. Conclusion

This study found that the MeOH extract of *M. malabathricum* had the highest TPC and TFC values, which corresponded to its significant antioxidant capacities, such as DPPH (8.58 ± 0.03 μg/mL), ABTS (4.59 ± 0.03 μg/mL), and FRAP (51.15 ± 0.10 μM Fe^{2+}/g). A positive relationship between TPC, TFC, and antioxidant data supported the analysis. *In vitro* anti-α-glucosidase and anti-α-amylase activities of the methanolic extract of leaves were reported for the first time. *In vitro* antidiabetic testing showed that the methanolic extract inhibited α-glucosidase and α-amylase with IC_{50} values of 75.25±1.60 and 52.38±1.32 μg/mL, respectively. The IC_{50} values of anti-α-glucosidase and anti-α-amylase were 9 and 6-fold higher than the positive control (acarbose), respectively. Many plants have been known to contain substances such as flavonoids, terpenoids, glycosides, etc, which are often associated with antidiabetic effects. This complies with the test results for the total phenolic content (TPC) and total flavonoid content (TFC) of the methanol extract of *M. malabathricum* leaves, which are quite high. A dose of 200 mg/Kg body weight of the methanolic extract reduced rats' blood glucose rate and serum blood glucose by 51.01±11.12% and 37.82%, respectively, after 15 days of treatments. These findings suggested that methanolic extract of *M. malabathricum* leaves can be a potential source of antioxidant and antidiabetic agents. The limitation of this study was that extract from *M. malabathricum* leaves was used only for bioactivity tests focused on antioxidants (DPPH, ABTS, and FRAP) *in vitro* (anti-α-glucosidase and anti-α-amylase) and *in vivo* antidiabetic. The results from this study provide a reference for the

development of further studies on the benefits of *M. malabathricum* leaves as antidiabetic drugs. The combination of methanol extract with other antidiabetic drugs can increase the antidiabetic activity of the methanol extract.

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