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α-Glucosidase Inhibitory and A Leptospermone Derivative from *Rhodomyrtus tomentosa*

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Abstract: *One of the treatments for diabetes mellitus disease is to control blood sugar level using an inhibitor of α-glucosidase enzyme. The methanol extracts of the fruit, stem, and leaves of* Rhodomyrtus tomentosa *were found significant in inhibiting α-glucosidase with an* IC_{50} *value of 20.57, 20.36 and 43.99 μg/mL respectively. The ethyl acetate and n-butanol fractions from the methanol extract of* R. tomentosa *fruit exhibited the potent inhibition (*IC_{50} *13.49 and 19.29 μg/mL) compare to acarbose and n-hexane fraction (*IC_{50} *383.68 and 1175.16 μg/mL). A leptospermone derivative, rhodomyrtosone D, was isolated from the ethyl acetate fraction of* R. tomentosa *fruit. The structure of rhodomyrtosone D was identified based on spectroscopic analysis, as well as comparing with literature data. The α-glucosidase inhibition of rhodomyrtosone D (*IC_{50} *110.45 μg/mL) was 3.5 fold more potent than acarbose. Thus,* R. tomentosa *plant could be potential as a natural resource of α-glucosidase inhibitor.*

Keywords: *α-glucosidase;* Rhodomyrtus tomentosa*; antidiabetic; rhodomyrtosone D; ethyl acetate fraction*

INTRODUCTION

Diabetes mellitus (DM) is a group of metabolic disorder, in which there are high blood sugar levels (hyperglycemia) over a prolonged period [1]. It will happen if the pancreas does not produce enough insulin that is able to convert sugar into energy, or the body's cells do not respond well to the insulin produced. Some serious complication of hyperglycemia such as cardiovascular disease, damage to the eyes, atherosclerosis, and chronic kidney disease (nephropathy) can also occur [2-3]. The control of blood sugar level by inhibition of carbohydrate-hydrolyzing enzymes in the digestive organ is believed to be important in hyperglycemia treatment [1]. The α-glucosidase, an enzyme in the small intestine, is responsible for the degradation of carbohydrate. The α-glucosidase inhibitor will interfere with the digestion of carbohydrate and thereby reduce the postprandial glucose level and insulin responses in a diabetic patient [2,4]. Acarbose, miglitol, and voglibose have been found as an α-glucosidase inhibitor and currently clinically used to control blood glucose of diabetic patients [5-6]. However, they have caused severe gastrointestinal side effects. Nowadays, natural resources have received tremendous attention as a therapeutic agent in the inhibition of α-glucosidase and have shown very promising biological activity.

Karamunting is locally named (Sumatera island) for *Rhodomyrtus tomentosa* and belonging to the Myrtaceae family. This plant is an evergreen shrub which is native to Southern Asia and Southeast Asia and is widely distributed in Indonesia. *R. tomentosa* is widely used as traditional medicines to treat a variety of disease caused by bacteria such as diarrhea, dysentery, and urinary tract infections [7-8]. In addition, its ripe fruits are used to boost the immune system [9]. Biologically, ethanolic extract of *R. tomentosa* fruits possesses potent antioxidant activities on DPPH radical scavenging

activity, reducing power as well as inhibition of lipid peroxidation activity [10] Furthermore, some extract of this plants were reported to have antibacterial and anti-hepatitis properties [11]. Chemically, various secondary metabolites have been reported, such as polyketide, flavonoids, anthocyanins, stilbenoids, and triterpenoids [9-13]. Rhodomyrtone, a phloroglucinol polyketide from *R. tomentosa* have displayed significant antibacterial activities against Gram-positive bacteria and suggested as a new candidate as a natural antibacterial drug [12,14].

Meanwhile, tomentosone A, hexacyclic phloroglucinol was reported as antimalarial against chloroquine-resistant and sensitive strains of *Plasmodium falciparum*. Resveratrol and piceatannol, a stilbenoid compound has been characterized by this plant [9]. A stilbenoid compound from *Syagrus romanzoffiana* was reported as a potential hypoglycemic agent. However, there is no literature on the α-glucosidase inhibitory of *R. tomentosa* and its bioactive chemical compound. In a search for potential α-glucosidase inhibitor from natural resources, the ability of *R. tomentosa* plant to inhibit the activity of the α-glucosidase enzyme as well as to isolate the bioactive compound have been investigated. One active compound, rhodomyrtosone D (**1**) was isolated, and its α-glucosidase inhibition was determined. The following describes the outcomes of these efforts.

■ EXPERIMENTAL SECTION

Materials

Rhodomyrtus tomentosa (fruits, leaves, and stem) were collected from Inderalaya, Ogan Ilir, South Sumatera. The plant was identified at Herbarium Anda, Department of Biology, University of Andalas. The solvents used, methanol, *n*-hexane, and ethyl acetate, were the technical grade that was distilled, while *n*-butanol and dimethylsulfoxide (DMSO) were pro analysis grade (p.a.) from Merck. The α-glucosidase (from *Saccharomyces cerevisiae*) and *p*-nitro-phenyl-α-D-glucopyranoside were purchased from Sigma-Aldrich. Bovine serum albumin (BSA) was purchased from Merck. Silica gel 60G (Merck) was used for vacuum liquid chromatography, and silica gel 60 PF_{254} (Merck) was used for radial chromatography. TLC analysis was performed on Kieselgel 60 GF_{254}, 0.25 mm aluminum plate (Merck) and visualized with cerium sulfate.

Instrumentation

Incubator Biosan PST-60HL was used for the sample incubation process. The absorbance of *p*-nitrophenol was measured by a Tecan Infinite F50 Microplate reader. The UV spectrum was recorded with Shimadzu UV-1240 spectrophotometer. IR spectrum was determined using KBr pellets on a Perkin Elmer FTIR Spectrum One spectrophotometer. ^{1}H-NMR (500 MHz) and ^{13}C-NMR (125 MHz) spectra were recorded with Agilent DD2 spectrometer, using residual and deuterated solvent peaks as reference standards.

Procedure

Extraction of sample for assay

As much as 100 g of each the dried powdered sample (fruits, leaves, and stem) of *R. tomentosa* were extracted by maceration method using methanol (400 mL) as the solvent at the room temperature. The maceration process was carried out three times (@ 24 h). The methanol solvents were evaporated in under reduce pressure to give crude extracts of methanol of fruit, leaves, and stem (4.6, 4.2 and 3.9 g respectively). The crude of methanol extract of fruit was partitioned successively with *n*-hexane, ethyl acetate, and *n*-butanol and produce of each fraction after the solvent was evaporated.

In-vitro *α-glucosidase inhibition assay*

The α-glucosidase assay has been performed using the spectrophotometric method as previously described [2,15] with slight modification. As much as 10 µL of the sample at various concentrations was added with 55 µL of 50 mM phosphate buffer (pH 6.8) and 10 µL of 10 mM *p*-nitrophenyl-α-D-glucopyranoside as the substrate. After preincubated for 5 min at 37 °C, 25 µL of 0.1 U/mL α-glucosidase (in the phosphate buffer pH 6.8 containing 0.1 mg/mL bovine serum albumin) was added. The mixture was then incubated for 30 min at 37 °C. After that, the stopped solution (100 µL of 200 mM Na_2CO_3) was added to the mixture. The absorbance of the *p*-nitrophenol released due to hydrolysis of the

substrate by the α-glucosidase was measured by a microplate reader at 405 nm. The blank solution was prepared by replaced sample solution by DMSO. Acarbose (Glucobay®) is used as a positive control. The percentage inhibition of α-glucosidase was calculated using the following equation:

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

The IC_{50} was calculated by linear regression equation analysis between concentration and percentage inhibition.

Extraction and Isolation of R. tomentosa *fruits*

The dried fruits (2 kg) was extracted with methanol (3 × 7 L, 24 h each) by maceration method. The methanol extract was concentrated under reduced pressure to give 1.1 L syrup, which was suspended in distilled water. This suspension was partitioned successively with *n*-hexane, ethyl acetate, and *n*-butanol to afford *n*-hexane, ethyl acetate, and *n*-butanol fractions. The ethyl acetate fraction (15 g) was fractionated by vacuum liquid chromatography on silica gel 60 G, eluting with *n*-hexane-ethyl acetate system with increment ethyl acetate gradually (9:1, 8:2, 7:3, 6:4, 4:6, 2:8, 1:9, and 0:10, each 150 mL) to give 8 fractions (A-H). Fraction C (374 mg) was further separated using radial chromatography over silica gel 60 PF_{254} (1 mm), eluted with *n*-hexane-ethyl acetate gradually (85:15, 80:20, 75:25, 70:30, 60:40, 50:50) to yield a leptospermone derivative 1 (8.9 mg).

■ RESULTS AND DISCUSSION

The α-Glucosidase Inhibition of Extracts and Fractions

The extraction of three parts of *R. tomentosa*, namely, fruit, stem, and leaves produced methanol extract of 4.6, 3.9, and 4.2 g, respectively. All of these extracts were tested for the α-glucosidase inhibitory using *p*-nitrophenyl-α-D-glucopyranoside as the substrate and acarbose as the reference or positive control. The concentration of a substance that is required for 50% inhibition of α-glucosidase enzyme represented as IC_{50}. The methanol extract from the stem and fruit have a similar ability to inhibit α-glucosidase activity with the IC_{50} value were 20.36 and 20.57 µg/mL, respectively. Both of these extracts demonstrated two times more potent than the leaves methanol extract with the IC_{50} value was 43.99 µg/mL (Fig. 1). Base on the IC_{50} value, all three methanol extracts possessed high potency in inhibiting α-glucosidase compare to the reference drug, acarbose with the IC_{50} 383.68 µg/mL (Table 1).

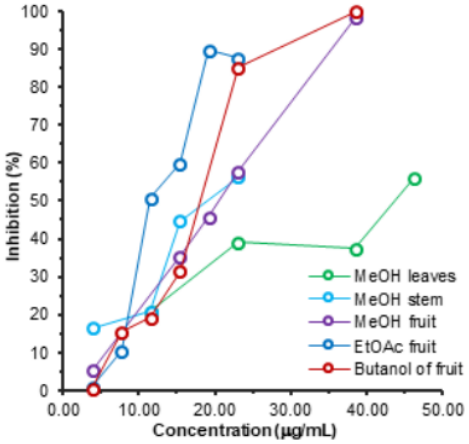

Fig 1. Effect of extracts and fractions on the inhibition of α-glucosidase

Table 1. Inhibitory effect of the extract, fraction and compound on α-glucosidase activity

Extract/compound	Inhibitor concentration (IC_{50}, µg/mL)
MeOH extract of the leaves	43.99
MeOH extract of the stem	20.36
MeOH extract of the fruit	20.57
n-hexane fraction of the fruit	1175.16
Ethyl acetate fraction of the fruit	13.49
n-butanol fraction of the fruit	19.29
Compound **1**	110.45
Acarbose*	383.68

*positive control

Previously, it has been reported that *R. tomentosa* fruit contains stilbenoid compound, such as resveratrol, and piceatannol [9]. These stilbenoids showed the more potent inhibition of α-glucosidase activity with IC_{50} 91 and 60 μg/mL respectively than acarbose with IC_{50} 247 μg/mL [5]. In addition, other phenolic compounds such as flavonoid isolated from *Morus alba* and anthocyanins isolated from noble muscadine grapes have been reported as a potential α-glucosidase inhibitory [16-17]. Meanwhile, the triterpenoid saponins from *Gypsophila oldhamiana* and highly oxygenated triterpenoid from *Fagara tessmannii* and *Luculia pinceana* also showed significant α-glucosidase inhibitory comparing to acarbose [1,18].

Based on its inhibition of α-glucosidase, the methanol extract of fruits was partitioned into *n*-hexane, ethyl acetate, and *n*-butanol. Ethyl acetate fraction had the highest α-glucosidase inhibitory with the IC_{50} of 13.49 μg/mL than an n-butanol fraction with the IC_{50} of 19.29 μg/mL due to its phenolic or stilbenoid content, meanwhile, the *n*-hexane fraction was not as potent as α-glucosidase inhibitory with the IC_{50} of 1175.16 μg/mL (Table 1 and Fig. 1). Compounds typically found in *n*-hexane fractions of *R. tomentosa* are nonpolar terpenoid like meroterpenoid and steroid [20]. These type of compound are usually inactive as an inhibitor of α-glucosidase. Meanwhile, oxygenated triterpenoid such as ursolic acid which found from a polar fraction of the leaves of *R. tomentosa* was reported as an inhibitor α-glucosidase [1,21].

Isolation and Structural Elucidation

The sequential partition to the methanol crude extract of *R. tomentosa* fruits (87 g) yielded *n*-hexane, ethyl acetate and *n*-butanol fraction of 1.54, 17.81 and 0.44 g, respectively. Ethyl acetate fraction with the highest α-glucosidase inhibition was chromatographed over silica gel with some chromatographic technique to afford compound **1**.

Compound **1** was isolated as a white powder with m.p. 120–121 °C. The UV spectrum in methanol showed the maximum absorption at 242 nm, which indicated the presence of α,β carbonyl unsaturated. The IR spectrum displayed absorption for the isolated carbonyl group at 1715 cm^{-1} as well as conjugated carbonyl group at 1678 and 1663 cm^{-1}, which consisted of the UV spectrum. In addition, there is absorption for C-H aliphatic group in 2976 and 2941 cm^{-1}. The ^{13}C-NMR (125 MHz, $CDCl_3$) was showed the presence of 14 signal. The two signals confirmed the existence of the isolated and conjugated carbonyl at δ_C 212.2 ppm and δ_C 192.2 ppm respectively. In addition, ^{13}C-NMR displayed the presence of five other quarternary carbon signal (δ_C 175.5 (oxy-carbon), 128.3, 113.2, 56.6, and 45.3 ppm), two signal for methine carbon (δ_C 46.6 and 34.5 ppm), and five signal for methyl carbon (δ_C 25.9, 24.5, 24.0, 22.4 and 15.6 ppm). The intensity of quarternary carbon signal at 128.3 ppm with the six other quarternary carbon (included the carbonyl) which has a ratio of 1:2, indicating that the six quarternary carbon is equivalent to twelve carbon. Furthermore, the five methyl carbon signals have an intensity ratio of 2:1 with a carbon methine signal at δ_C 34.5 ppm, consequently each of these methyl signals is identical for 2 methyl carbon (there are a total of 10 methyls). Based on this, compound **1** has 25 carbon atoms. The ^{1}H-NMR (500MHz, $CDCl_3$) spectrum exhibited the presence of a singlet signal of methine proton at δ_H 4.67 ppm. The spectrum also indicated the presence of an isopropyl unit with the appearance of a doublet signal at δ_H 1.00 ppm (6H, *d*, *J* = 6.9 Hz, 2xCH_3) which is adjacent to the methine proton at δ_H 2.35 ppm (1H, *sept*, *J* = 6.9 Hz). This constant coupling value indicates that both signals are correlated to each other as vicinal aliphatic protons.

In addition, there are three singlet signals at δH 1.41 (12H), 1.32 (6H), and 1.25 ppm (6H) which indicate the presence of 8 methyl groups. The HMBC correlation revealed a correlation of both methyl on a geminal dimethyl group (δ_H 1.25 and 1.32 ppm) to the isolated and conjugated carbonyl group (δ_C 212.2 and 192.2 ppm) as well as correlation of both methyl on another geminal dimethyl group to the isolated carbonyl (δ_C 212.2 ppm) and oxy-carbon (δ_C 175.5 ppm). These explained that both of geminal dimethyl is α position in β-triketone unit. Based on the previous NMR data, there are two symmetrical units of β-triketone. Furthermore,

Table 2. NMR data of compound **1** in $CDCl_3$ and rhodomyrtosone D

No	Compound 1			Rhodomyrtosone D [17]	
	δC	δ_H (ΣH, *mult*, J_{Hz})	HMBC (H→C)	δ_C	δ_H (*mult*, J_{Hz})
1 (1')	192.2	-	-	192.4	-
2(2')	56.6	-	-	56.4	-
3(3')	212.2	-	-	212.1	-
4(4')	45.3	-	-	45.2	-
5(5')	175.5	-	-	175.7	-
6(6')	113.2	-	-	113.0	-
7(7')	25.8	1.25 (6H, *s*)	C-3(3'), C-1(1'), C-2(2'), C-8(8')	25.7	1.27 (*s*)
8(8')	22.4	1.32 (6H, *s*)	C-3(3'), C- 1 (1'), C-2(2'), C-7(7')	22.3	1.34 (*s*)
9(9')	24.0	1.41 (6H, *s*)	C-3(3'), C-5(5'), C-4(4'), C-9(9'), C-10(10')	23.9	1.44 (*s*)
10(10')	24.5	1.41 (6H, *s*)	C-3(3'), C-5(5'), C-4(4'), C-9(9'), C-10(10')	24.4	1.44 (*s*)
1''	46.6	4.67 (1H, *s*)	C-5(5'), C-2'', C-6(6'), C-3''	46.5	4.69 (*s*)
2''	128.3	-	-	128.2	-
3''	34.5	2.35 (1H, *sept*, 6.9)	C-2'', C-1'', C-4'', C-5''	34.4	2.37 (*sept*, 6.9)
4'', 5''	15.6	1.00 (6H, *d*, 6.9)	C-2'', C-3'', C-4', C-5''	15.5	1.02 (*d*, 6.9)

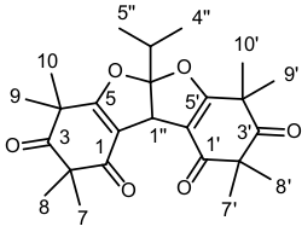

Fig 2. Structure of compound **1** (rhodomyrtosone D)

the correlation between of proton δ_H 4.67 ppm to isopropyl unit (δ_C 34.5 ppm) and oxy-carbon (δ_C 175.5 and 128.3 ppm) indicating that the isopropyl group was an adjacent bis-furan ring and the bis-furan ring was integrated with the β-triketone unit. According to this spectroscopic evidence (Table 2) and comparing to those of reported literature [17], the structure of compound **1** was established as rhodomyrtosone D (Fig. 2). This compound has been previously reported from *R. tomentosa* leaves [17].

The isolated compound **1** (rhodomyrtosone D) was examined for α-glucosidase inhibitory activity with concentration range about 30.77 to 0.24 μg/mL. The percentage of α-glucosidase inhibition from rhodomyrtosone D at the maximum test concentration of 30.77 μg/mL was 17.7%, while the inhibition of acarbose at the same concentration was 8.54%. Using the extrapolation method to linear regression, the IC_{50} of rhodomyrtosone D in inhibiting α-glucosidase was 110.45 μg/mL. This IC_{50} is lower compared to acarbose. Based on these values, rhodomyrtosone D has the ability to inhibit α-glucosidase enzyme stronger than acarbose.

■ CONCLUSION

The leaves, stem, and fruit of *R. tomentosa* plant were potential as a source of a natural antidiabetic, especially from the ethyl acetate fraction of the fruit. A bioactive compound, rhodomyrtosone D, was isolated from the fruit of *R. tomentosa* and showed higher α-glucosidase inhibition 3.5 fold than acarbose.

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