

Research Article **α-Amylase and α-Glucosidase Inhibitory Saponins from Polyscias fruticosa Leaves**

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Three bisdesmosidic saponins 3-O-[β -D-glucopyranosyl-(1 \rightarrow 4)- β -D-glucuronopyranosyl] oleanolic acid 28-O- β -D-glucopyranosyl-oleanolic acid 28-O- β -D-glucopyranosyl-(1 \rightarrow 2)-[β -D-glucopyranosyl-(1 \rightarrow 4)]- β -D-glucuronopyranosyl-(1 \rightarrow 2)-[β -D-glucopyranosyl-(1 \rightarrow 4)]- β -D-glucuronopyranosyl-oleanolic acid 28-O- β -D-glucopyranosyl-(1 \rightarrow 2)- β -D-glactopyranosyl ester (3) were isolated from a methanol extract of *Polyscias fruticosa* (L.) Harms leaves. Compound 1 was obtained as a main constituent and compound 3 was reported for the first time and named as polyscioside I. Saponin 1 inhibited porcine pancreas α -amylase and yeast α -glucosidase activities while 2 and 3 were inactive. Synergistic inhibitory effect on α -amylase was observed from the combination of low concentrations of 1 and acarbose. The findings suggest the use of *P. fruticosa* and its major saponin 1 for the prevention and treatment of diabetes and its complications.

1. Introduction

Polyscias fruticosa (L.) Harms (synonyms Nothopanax fruticosus (L.) Miq. and Panax fruticosus L.), belonging to the family Araliaceae, is widely used in Vietnam as a tonic agent for the treatment of ischemia and inflammation and to increase blood flow in the brain. The leaves of this plant are also eaten as a salad [1]. Previous studies showed that P. fruticosa leaf extracts exhibited antipyretic, antiinflammatory, analgesic, and molluscicidal properties [2, 3] and antidiabetic activity [4]. A few reports on the chemical composition of this plant indicated the presence of polyacetylene [5] and saponins [6]. Diabetes is a group of metabolic diseases characterized by chronic hyperglycemia resulting from deficiency in insulin secretion or action. Recent reports revealed that a high postprandial plasma glucose level is more harmful than fasting blood glucose. Therefore, it is important to control the postprandial blood glucose level to reduce complications and mortality. One therapeutic approach for treating diabetes is to decrease postprandial glycemia by inhibiting enzymes responsible for carbohydrate hydrolysis, such as α -glucosidase and α -amylase [7].

Our search for antidiabetic agents of natural origin identified a methanol extract of P. fruticosa leaves that showed significant inhibitory activity against α -glucosidase and α -amylase. A phytochemical investigation of the methanol extract of P. fruticosa leaves led to the isolation of three bisdesmosidic saponins (Figure 1). Their structures were elucidated as 3-O-[β -D-glucopyranosyl-(1 \rightarrow 4)- β -D-glucuronopyranosyl] oleanolic acid 28-O-β-D-glucopyranosyl ester (1) [6, 8], 3-O-{ β -D-glucopyranosyl-(1 \rightarrow 2)-[β -D-glucopyranosyl- $(1\rightarrow 4)$]- β -D-glucuronopyranosyl} oleanolic acid 28-O- β -D-glucopyranosyl ester or polyscioside D (2) [6], and 3-O-{ β -D-glucopyranosyl-(1 \rightarrow 2)-[β -D-glucopyranosyl- $(1\rightarrow 4)$]- β -D-glucuronopyranosyl} oleanolic acid 28-O- β -Dglucopyranosyl- $(1\rightarrow 2)$ - β -D-galactopyranosyl ester (3), newly named polyscioside I. All compounds were evaluated for their inhibitory activity against porcine pancreas α -amylase and yeast α -glucosidase.

2. Experimental

2.1. *General Experimental Procedures*. Optical rotation values were recorded a JASCO P-2000 digital polarimeter (JASCO,



FIGURE 1: Structure of compounds 1-3 and key HMBC correlations of 3.

Tokyo, Japan). NMR experiments were carried out on a Bruker AM500 FT-NMR spectrometer (Bruker, Rheinstetten, Germany) using tetramethylsilane (TMS) as internal standard. The HR-ESI-MS was recorded on API Q-STAR PULSAR I of Applied Biosystem. The bioassay absorbance was read by xMark Microplate Spectrophotometer reader (Bio-Rad Laboratories, USA).

2.2. Plant Material. The leaves of Polyscias fruticosa were collected in Tien Hai, Thai Binh, in July 2011 and identified by Professor Tran Huy Thai, Institute of Ecology and Biological Resources, Vietnam Academy of Science and Technology. The voucher specimens were deposited at the herbarium of the Institute of Ecology and Biological Resources.

2.3. Extraction and Isolation. The air-dried and powdered *P*. *fruticosa* leaves (2.0 kg) were extracted with methanol (5 L × 3 times) at room temperature. The combined extracts were concentrated to give 300 g of crude extract, which was then resuspended in water (1.5 L) and successively partitioned with hexane and ethyl acetate (each $0.5 L \times 3$ times) to obtain 75

and 92 g of hexane and ethyl acetate residues, respectively. The water residue was filtered through a Diaion HP-20 column eluted by 0%, 25%, and 100% methanol in water. The 100% methanol-eluted fraction was diluted with water (1:1 v/v) and kept overnight at 4°C. Compound 1 as white crystals (500 mg) was obtained by filtering. The filtrate was concentrated and chromatographed on a silica gel column eluted with a gradient of 0%, 50%, and 100% methanol in ethyl acetate to afford three fractions, F1–F3. Fraction F2 was fractionated on a silica gel column eluted with chloroformmethanol-water (50:10:1 v/v) to afford compound **2** (10 mg). Compound **3** (20.5 mg) was purified from F3 by a RP-18 column (methanol-water 1:1 v/v).

Polyscioside I (3). White powder, mp. >300°C. $[\alpha]_D^{24} = +12.4$ (*c* 0.1, MeOH). ¹H NMR (500 MHz, DMSO-*d*₆): δ 0.67 (3H, br s, H-26), 0.73 (3H, br s, H-24), 0.85 (6H, br s, H-25, 29), 0.87 (3H, br s, H-30), 0.97 (3H, br s, H-23), 1.06 (3H, br s, H-27), 3.01 (1H, m, H-3), 3.60 (1H, m, H-2^{''}), 4.25 (1H, *d*, *J* = 7.0 Hz, H-1^{''}), 4.29 (1H, *d*, *J* = 6.5 Hz, H-1'), 4.62 (1H, *d*, *J* = 7.5 Hz, H-1^{'''}), 4.48 (1H, *d*, *J* = 7.0 Hz, H-1^{'''}), 5.14 (1H, m, H-11), 5.30 (1H, *d*, *J* = 8.0 Hz, H-1^{'''}). ¹³C NMR (125 MHz,

DMSO- d_6): see Table 1. HR-ESI-MS (positive): m/z 1281.6127 [M + H]⁺, (calcd. 1281.6116 for C₆₀H₉₇O₂₉).

Acid Hydrolysis of **3**. Compound **3** (10 mg) was heated in 2 N HCl (5 mL) at 80°C for 2 h, and then the solution was extracted with ethyl acetate (2 mL \times 3). The sugar products in the aqueous layer were identified as glucose (Rf 0.65), galactose (Rf 0.60), and glucuronic acid (Rf 0.12) in comparison with standards by silica gel thin layer chromatography (developed with acetone-methanol-water 10:9:1 and sprayed by 10% sulfuric acid solution containing 2% vanillin). After preparative thin layer chromatography, the optical rotation of each sugar fraction was checked. The positive optical rotation values led to the assignment of D-glucuronic acid, D-glucose, and D-galactose [9].

2.4. Assay for α -Glucosidase Inhibition. The yeast α -glucosidase (G0660, Sigma-Aldrich) enzyme inhibition assay was performed by the digestion of *p*-nitrophenyl- α -Dglucopyranoside [10]. The sample solution (2 μ L dissolved in DMSO) and 0.5 U/mL α -glucosidase (40 μ L) were mixed in 120 μ L of 0.1 M phosphate buffer (pH 7.0). After 5 min preincubation, 5 mM *p*-nitrophenyl- α -D-glucopyranoside solution (40 μ L) was added and the solution was incubated at 37°C for 30 min. The absorbance of released 4-nitrophenol was measured at 405 nm by using a microplate reader (Molecular Devices, CA). Acarbose was used as positive control (IC₅₀ 650.4 μ g/mL).

2.5. Assay for α -Amylase Inhibition. The porcine pancreas α -amylase (A3176, Sigma-Aldrich) enzyme inhibitory activity was measured using the method reported by Ashok Kumar et al. [11] with slight modifications. Substrate was prepared by dissolving 2-chloro-4-nitrophenyl- α -D-maltotrio side (93834, Sigma-Aldrich) in phosphate buffer (pH 7.0). The sample (2 μ L dissolved in DMSO) and 0.5 unit/mL α -amylase (50 μ L) were mixed in 100 μ L of 0.1 M phosphate buffer (pH 7.0). After 5 min preincubation, substrate solution (50 μ L) was added and the solution was incubated at 37°C for 15 min. The absorbances were measured at 405 nm. Acarbose was used as positive control (IC₅₀ 57.6 μ g/mL).

3. Results and Discussion

Compound **3** was obtained as a white crystal and its high-resolution electrospray ionization mass spectrometry spectrum revealed an ion peak at m/z 1281.6127 [M + H]⁺, corresponding to the molecular formula $C_{60}H_{96}O_{29}$. The ¹H-NMR spectrum of **1** showed seven methyl groups at $\delta_{\rm H}$ 0.67 (3H, br s, H-26), 0.73 (3H, br s, H-24), 0.85 (6H, br s, H-25, 29), 0.87 (3H, br s, H-30), 0.97 (3H, br s, H-23), and 1.06 (3H, br s, H-27) and five glycosidic anomeric protons at $\delta_{\rm H}$ 4.25 (1H, d, J = 7.0 Hz, H-1"), 4.29 (1H, d, J = 6.5 Hz, H-1'), 4.48 (1H, d, J = 7.0 Hz, H-1"), 5.30 (1H, d, J = 8.0 Hz, H-1"), and 4.62 (1H, d, J = 7.5 Hz, H-1"). The large coupling constants of all anomeric protons indicated the β -configuration of the sugars. ¹³C-NMR and DEPT spectra indicated the presence of an olean triterpene skeleton with

С	1	2	3	С	1	2	3
1	38.1	38.1	38.1	3-O-GluA			
2	25.4	22.9	25.4	1'	105.0	103.6	103.6
3	87.9	88.4	88.3	2′	73.5	79.3	79.5
4	38.7	38.6	38.6	3'	75.4	75.4	75.3
5	55.0	55.0	55.0	4'	82.9	82.3	82.3
6	17.7	17.7	17.7	5'	75.3	75.1	75.1
7	32.2	32.3	32.7	6′	172.0	171.8	171.5
8	40.0	40.7	40.0	4'-O-Glu			
9	47.0	47.0	47.0	1″	103.8	103.3	103.3
10	36.2	36.2	36.2	2″	73.4	73.5	73.6
11	22.9	22.9	22.9	3″	76.3	76.2	76.3
12	121.6	121.7	121.5	$4^{\prime\prime}$	70.0	69.9	69.9
13	143.4	143.4	143.5	5″	77.0	77.0	77.0
14	41.2	41.2	41.1	6″	61.1	61.1	61.0
15	27.1	27.7	27.9	2'-O-Glu			
16	22.5	22.5	21.9	1''''	_	103.1	103.2
17	45.9	45.9	45.8	2''''	_	73.5	73.6
18	40.7	40.7	40.7	3''''	_	76.1	76.0
19	45.5	45.5	45.5	4''''	_	70.1	70.0
20	30.2	30.3	30.2	5''''	_	76.8	76.7
21	33.2	33.2	33.2	6''''	_	60.9	61.0
22	31.6	31.6	32.3	28-O-Glc/Gal			
23	27.6	27.7	27.7	1'''	94.1	94.1	91.9
24	16.6	16.1	16.7	2′′′	72.3	72.3	76.9
25	15.1	15.1	15.1	3′′′	76.6	76.6	74.1
26	16.4	16.9	16.7	4'''	69.5	69.5	70.7
27	25.4	25.5	25.5	5‴	77.6	77.7	76.8
28	175.2	175.2	175.2	6'''	60.7	60.7	61.8
29	32.7	32.7	32.7	2'''-O-Glu			
30	23.3	23.3	23.4	1'''''	_	_	102.3
				2'''''	_	_	75.0
				3'''''	_	_	77.0
				4'''''	_	_	69.4
				5'''''	_	_	77.5
				6'''''	_	_	60.5

seven CH₃, ten CH₂, five CH, and 8 C signals (Table 1). The aglycone was identified as oleanolic acid, a common triterpene of saponins in the genus *Polyscias* [6]. The $\delta_{\rm C}$ values of C-3 at $\delta_{\rm C}$ 88.3 and C-28 at $\delta_{\rm C}$ 175.2 suggested that compound **3** was a bisdesmosidic saponin with sugar units attached to these positions. In addition, five sugar moieties were recognized by five anomeric methine groups at $\delta_{\rm C}$ 103.6 (C-1'), 103.3 (C-1''), 91.9 (C-1'''), 103.2 (C-1''''), and 102.3 (C-1''''). These data are similar to those of compound **2**,

except for the addition of a sugar moiety and the upfield shift of the anomeric signal at $\delta_{\rm C}$ from 94.1 to 91.9. Acid hydrolysis of compound 3 allowed the identification of D-glucuronic acid, D-glucose, and D-galactose. Extensive analysis of the HMBC spectrum of compound 3 allowed the position of the sugar units to be determined. The couplings from H-1' $(\delta_{\rm H} 4.29)$ to C-3 $(\delta_{\rm C} 88.3)$ indicated that the glucuronic and glucosyl moieties attached to C-3. The correlations from H-1" ($\delta_{\rm H}$ 4.25) to C-4' ($\delta_{\rm C}$ 82.3) and between H-4"" ($\delta_{\rm H}$ 4.48) and C-2' ($\delta_{\rm C}$ 79.5) confirmed that the two glucosyl units were attached to C-2' and C-4', respectively. Indeed, the ¹³C-NMR data of this fragment coincided well with the β -D-glucopyranosyl- $(1\rightarrow 2)$ - $[\beta$ -D-glucopyranosyl- $(1\rightarrow 4)$]- β -Dglucuronopyranosyl of compound 2 (Table 1). The HMBC correlations from H-1^{'''} ($\delta_{\rm H}$ 5.31) to C-28 ($\delta_{\rm C}$ 175.2) and the anomeric C-1^{'''} resonance shifted upfield at $\delta_{\rm C}$ 91.9 suggesting the galactose unit attached to C-28. The HMBC couplings from H-1^{''''} ($\delta_{\rm H}$ 4.62) to C-2^{'''} ($\delta_{\rm C}$ 76.9) and from H-2^{'''} ($\delta_{\rm H}$ 3.60) to C-1^{'''''} ($\delta_{\rm C}$ 102.3) and the COSY crosspeak between H-1^{'''} and H-2^{'''} indicated that the glucose unit attached to C-2". Thus, compound 3 was elucidated as 3-O-{ β -D-glucopyranosyl-(1 \rightarrow 2)-[β -D-glucopyranosyl-(1 \rightarrow 4)]- β -D-glucuronopyranosyl} oleanolic acid 28-O- β -Dglucopyranosyl- $(1\rightarrow 2)$ - β -D-galactopyranosyl ester, named polyscioside I.

The inhibitory effects of the isolated compounds against porcine pancreas α -amylase and yeast α -glucosidase were evaluated in comparison with the antidiabetic acarbose (Table 2). Compound 1 potently inhibited α -amylase and α glucosidase with IC₅₀ values of 27.1 and 440.5 μ g/mL, respectively. In contrast, compounds 2 and 3 did not show any effect on both enzymes. Dou et al. reported that the glucuronic acid unit at C-3 and glucosidic moiety at C-28 of the aglycone were the functional groups essential for α -amylase and α glucosidase inhibition; the addition or replacement of glucose by another sugar unit might thus abolish the inhibitory activity [12]. In oral sucrose tolerance tests, several oleanolic acid glycosides showed significant antihyperglycemic activity in the oral sucrose tolerance in rats [13, 14]. However, the 2'- $O-\beta$ -D-glucopyranosyl unit attached to the glucuronic acid moiety was assumed to markedly reduce the hypoglycemic effect [15]. Consistent with this, in our study, compounds 2 and 3 possessing a 2'-O- β -D-glucopyranosyl unit were inactive regarding α -amylase and α -glucosidase inhibition. Previous studies showed that P. fruticosa leaf extracts strongly inhibited rat intestinal α -glucosidase [16] and exhibited hypoglycemic and antihyperglycemic activity in normal and streptozotocin-diabetic albino rats [4]. Our results suggest that the observed hypoglycemic activity might be related to the inhibition of α -amylase and α -glucosidase enzymes.

It was of interest to establish whether compound 1 and acarbose interact synergistically or additively in the inhibition of α -glucosidase and α -amylase. Therefore, the assay was performed in solutions containing these agents alone or in a mixture at different concentrations. The results showed that the combination of compound 1 and acarbose produced a synergistic inhibitory effect on porcine pancreas α -amylase (Figure 2) but had no effect on yeast α -glucosidase (data not shown). Interestingly, higher synergistic inhibition

TABLE 2: Inhibitory effects (IC₅₀ \pm SD, μ g/mL) of 1–3 for α -amylase and α -glucosidase.

Compounds	α-Amylase	α-Glucosidase
1	27.1 ± 2.05	440.5 ± 12.7
2	_	_
3	—	_
Acarbose	57.6 ± 4.12	650.4 ± 33.4

was found from the combination of low concentrations of individual agents. At 1.0 μ g/mL, compound 1 and acarbose alone exhibited only 1.5% and 4.2% inhibition, respectively. However, their combination increased the inhibition up to 32.8%. At a higher concentration of 10 μ g/mL, the percentage of α -amylase inhibition of the mixture was equal to the sum of compound 1 and acarbose, suggesting that they produced additive inhibition. A slight increase in inhibition was obtained from the mixture in comparison with that achieved by the individual agents at 100 μ g/mL. These findings indicate that saponin 1 produced synergistic effects on porcine pancreas α -amylase inhibition when combined with a low concentration of acarbose.

Acarbose is a potent α -glucosidase inhibitor and has been used in the treatment of type 2 diabetes. It can also be used in combination with other agents, such as sulfonylurea and metformin, in patients with diabetes. However, the long-term use and high-dose administration of this drug cause severe side effects, such as diarrhea, flatulence, and abdominal or stomach pain [17–19]. Our study showed that the combination of *P. fruticosa* saponin 1 with acarbose at a low concentration produced more synergistic inhibition than either drug alone, suggesting that they might provide a significant clinical benefit in delaying postprandial hyperglycemia and diminishing the adverse effects of acarbose.

4. Conclusion

Three bisdesmosidic saponins, including two known 3-O-[β -D-glucopyranosyl-(1 \rightarrow 4)- β -D-glucuronopyranosyl] oleanolic acid 28-O- β -D-glucopyranosyl ester (1) and 3-O-{ β -D-glucopyranosyl-(1 \rightarrow 2)-[β -D-glucopyranosyl-(1 \rightarrow 4)]- β -D-glucuronopyranosyl} oleanolic acid 28-O- β -D-glucopyranosyl-(1 \rightarrow 2)-[β -D-glucopyranosyl-(1 \rightarrow 4)]- β -D-glucopyranosyl-(1 \rightarrow 2)-[β -D-glucopyranosyl-(1 \rightarrow 4)]- β -D-glucuronopyranosyl} oleanolic acid 28-O- β -D-glucopyranosyl-(1 \rightarrow 2)-[β -D-glucopyranosyl-(1 \rightarrow 4)]- β -D-glucuronopyranosyl} oleanolic acid 28-O- β -D-glucopyranosyl(1 \rightarrow 2)- β -D-glactopyranosyl ester (named polyscioside I, 3), were isolated from the leaves of *P. fruticosa*. Compound 1 showed inhibitory effects against porcine pancreas α -amylase and yeast α -glucosidase activities and produced a synergistic effect with acarbose in α -amylase inhibition. Further study is needed to clarify the mechanism of enzyme inhibition as well as the hypoglycemic properties of saponin 1.

Competing Interests

The authors declare that there are no competing interests regarding the publication of this paper.



FIGURE 2: The percentage inhibition by combination of **1** and acarbose on porcine pancreatic α -amylase. Results are expressed as means ± SD; n = 3. *P < 0.05 compared with acarbose alone.

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