Papuabalanols A and B, New Tannins from *Balanophora papuana*

Takahiro Hosoya,[a] Asami Nakata,[a] Kazumasa Zaima,[a] Jalifah Latip,[b] Laily Bin Din,[b] Noramly Muslim,*[,b] and Hiroshi Morita*[,a]

[a] *Faculty of Pharmaceutical Sciences, Hoshi University; 2–4–41 Ebara, Shinagawa-ku, Tokyo 142–8501, Japan: and* [b] *School of Chemical Sciences and Food Technology, Faculty of Science and Technology, Universiti Kebangsaan Malaysia; 43600 Bangi, Selangor, Malaysia.*

Received December 10, 2009; accepted February 18, 2010; published online February 19, 2010

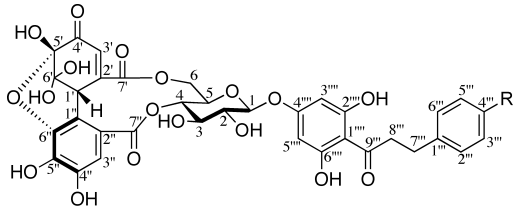
Two new dehydrohexahydroxydiphenoyl (DHHDP) esters of dihydrochalcone glycosides, papuabalanols A (1) and B (2) were isolated from the ethyl acetate extract of *Balanophora papuana*. Their structures were elucidated on the basis of spectroscopic data and chemical evidences. Papuabalanol A (1) showed moderate vasodilator effect on rat aorta and papuabalanol B (2) showed potent inhibition of mushroom tyrosinase and anti-melanogenesis in B16 mouse melanoma cells.

Key words *Balanophora papuana*; papuabalanol; dehydroellagitannin; tyrosinase inhibitory activity; anti-melanogenesis; vasodilator

The genus Balanophora (Balanophoraceae) comprising about 80 species is mainly distributed in the tropical and subtropical areas of Asia and Oceania. Among them, about 6 species are growing in peninsula Malaysia, particularly in Cameron highland. *Balanophora papuana* Schlechter is a holoparasitic flowering plant growing on roots of many species of plants. As parasitic plants, Balanophoraceae don't have chlorophyll so get all their nutrients and water from the host tree by means of a highly modified root system. Some with yellow, orange, red, and purple inflorescences that emerge from warty tubers attached to the roots of host plants. Plants are also an important part of Cameron highland ecosystem in Malaysia. The whole plants are used as traditional medicines for the treatment of hemorrhoids, stomachache, and hemoptysis in China, Japan, and Thailand.[1)]

Some hydrolysable tannins and steroids have been isolated from the extracts from *Balanophora* species,[2—6)] but no investigation on the chemical constituents of *B. papuana* has been reported. In the course of our continuing search for new bioactive natural products, we isolated two new dehydroellagitannin, papuabalanols A (**1**) and B (**2**) from *B. papuana*. Herein we report the isolation and structural characterization of papuabalanols A (**1**) and B (**2**) showing vasorelaxant and inhibition of tyrosinase activities, and anti-melanogenesis with B16 mouse melanoma cells.

Whole parts of the *B. papuana* were extracted with ethyl acetate, and the extract was subjected to an octadecyl silica (ODS) column (H_2O/MeOH) and a Sephadex LH-20 column (MeOH) followed by HPLC (H_2O/MeCN) to afford **1** and **2** together with (−)-pinoresinol (**3**)[7)] and ferulaldehyde.



1 : R=OH
2 : R=H

Chart 1

Papuabalanol A (**1**), $[\alpha]_D^{27}$ +39 (c=1.0, MeOH), was obtained as a yellow amorphous solid and its molecular formula was determined to be $C_{35}H_{30}O_{19}$ by HR-electrospray ionization (ESI)-MS [m/z 753.1280 $(M-H)^-$, Δ −1.75 mmu]. IR absorptions were indicative of the presence of hydroxyl group (3375 cm^{-1}), conjugated carbonyl (1716 cm^{-1}), and aromatic ring (1627, 1604 cm^{-1}). The UV absorption maxima at 280 and 222 nm were observed, suggesting the presence of a conjugated or an aromatic ring system. The ^{1}H-NMR data (Table 1) in acetone-d_6 showed the presence of seven aromatic protons (δ_H 7.07×2, 6.78, 6.72×2, 6.74, 6.14), six protons (δ_H 3.66—5.25) attached to a hydroxyl-bearing carbon, one methine proton (δ_H 4.73), two methylene protons (δ_H 3.35, 2.86), and a hydrogen bonded hydroxyl proton (δ_H 11.9). The ^{13}C-NMR data (Table 1) revealed thirty-five signals due to two ketonic carbons (δ_C 206.2, 192.0), two ester carbonyl carbons (δ_C 168.5, 164.9), 20 aromatic and olefinic carbons (δ_C 96.2—164.5), six sugar-derived carbons (δ_C 100.0, 75.2, 74.4, 74.0, 68.8, 66.0), two hemiacetal carbons (δ_C 96.6, 91.6), one methine carbon (δ_C 42.9), and two methylene carbons (δ_C 47.0, 30.0).

Analysis of its 2D NMR spectra revealed the presence of a dihydrochalcone, a dehydrohexahydroxydiphenoyl (DHHDP) group, and a glucose unit. The ^{1}H–^{1}H correlation spectroscopy (COSY) spectra of **1** showed the presence of two aromatic protons [H-2‴ (H-6‴) and H-3‴ (H-5‴)], two methylene protons (H-7‴/H-8‴), and sugar moiety protons (H-1—H-6). The heteronuclear multiple bond correlation (HMBC) correlations of H-7‴ to C-1‴, C-2‴ (C-6‴), and C-9‴, H-8‴ to C-1‴, C-7, and C-9‴, and H-3‴ to C-9‴, C-1‴, C-2‴, and C-5‴ suggested the presence of a *p*-substituted dihydrochalcone moiety. The HMBC correlation of H-1 (δ_H 5.25) of the glucose to C-4‴ (δ_C 164.5) of dihydrochalcone unit, and the characteristic chemical shift of the anomeric carbon (δ_C 100.0) suggested an *O*-glycosidic linkage at C-4‴. The ^{1}H- and ^{13}C-NMR data of **1** corresponded to those in dihydrochalcone-sugar moiety with a phloretin 4′-*O*-*β*-D-glucose except for C-4, C-5, and C-6.[8)] The HMBC correlations of H-1′ to C-2′, C-3′, C-5′, C-6′, C-7′, C-1″, C-2″, and C-6″, H-3′ to C-1′, C-2′, C-4′, and C-7′, and H-3″ to C-1″, C-4″, C-5″, and C-7″ revealed the presence of DHHDP group which was suggested to link at C-4 and C-6 with an ester linkage,

* To whom correspondence should be addressed. e-mail: moritah@hoshi.ac.jp; noramlymuslim@yahoo.com

Table 1. ^{1}H- and ^{13}C-NMR Data for Papuabalanols A (**1**) and B (**2**) in Acetone-d_6 at 300 K[a)]

Position	**1**		**2**	
	δ_H (int.; mult.; J (Hz))	δ_C	δ_H	δ_C
1	5.25 (1H, d, 7.6)	100.0	5.25 (1H, d, 7.6)	100.0
2	3.66 (1H, t, 8.0)	74.0	3.66 (1H, t, 8.0)	74.0
3	3.91 (1H, t, 10.6)	74.4	3.91 (1H, t, 10.5)	74.4
4	5.22 (1H, t, 9.2)	75.2	5.22 (1H, t, 10.2)	75.2
5	4.05 (1H, m)	68.6	4.06 (1H, m)	68.7
6	3.87 (1H, m)	66.0	3.88 (1H, m)	66.0
	5.01 (1H, dd, 4.8, 10.8)		5.02 (1H, dd, 4.7, 10.5)	
1′	4.73 (1H, s)	42.9	4.73 (1H, s)	42.9
2′		151.7		151.6
3′	6.78 (1H, s)	130.8	6.78 (1H, s)	130.8
4′		192.0		192.0
5′		96.6		96.6
6′		91.6		91.6
7′		164.9		164.9
1″		112.9		112.9
2″		124.4		124.3
3″	6.74 (1H, s)	108.1	6.73 (1H, s)	108.2
4″		146.1		146.1
5″		135.4		135.5
6″		142.4		142.3
7″		168.5		168.5
1‴		133.2		142.6
2‴(6‴)	7.07 (2H, d, 8.4)	130.1	7.26 (2H, m)	129.1
3‴(5‴)	6.72 (2H, d, 8.4)	115.9	7.26 (2H, m)	129.1
4‴		156.4	7.16 (1H, m)	126.6
7‴	2.86 (1H, t, 8.0)	30.0	2.97 (1H, t, 8.0)	31.3
8‴	3.35 (1H, t, 8.0)	47.0	3.41 (1H, t, 8.0)	46.5
9‴		206.2		205.9
1⁗		106.6		106.5
2⁗(6⁗)		164.1		164.1
3⁗(5⁗)	6.14 (1H, s)	96.2	6.15 (1H, s)	96.2
4⁗		164.5		164.5

a) δ in ppm.

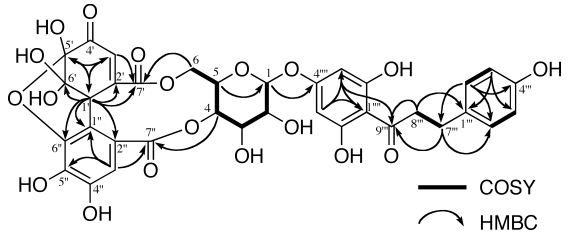


Fig. 1. Selected 2D NMR Correlations for Papuabalanol A (**1**)

respectively, by the HMBC correlations of H-6 to C-7′ (δ_C 164.9) and H-4 to C-7″ (δ_C 168.5). It is known that the dehydroellagitannin usually exists in solution as an equlibrium mixure of five- and six-membered hemiketal ring.[9)] Papuabalanol A (**1**) gave a broad collapsed peak in high-performance liquid chromatography (HPLC) in H_2O/MeOH solvent system, and the presence of two tautomers exist in CD_3OD solvent on NMR time scale. The DHHDP group in geraniin took two tautomeric isomers in acetone-d_6.[10)] The comparison of ^{13}C-NMR data between the DHHDP groups of papuabalanol A (**1**) and geraniin revealed that **1** took a single form with a six-membered hemiketal ring.

Acid hydrolysis of **1** gave a D-glucose as the sugar component, which was confirmed by comparing the retention time in HPLC analysis and optical rotation with those of an authentic sample. The β-anomeric configuration for a D-glucose was assigned from the $^{3}J_{H1,H2}$ coupling constant (J=7.6). The absolute configuration at C-1′ of DHHDP group of dehydroellagitannin was determined by the comparison of the circular dichroism (CD) spectral data. In the previous report,[11)] the CD spectrum of 4,6-*O*-[(1′*S*)-DHHDP]-D-glucose showed the positive Cotton effects at 375 ($\Delta\varepsilon$ +2.7) and 237 ($\Delta\varepsilon$ +7.8) nm, and the negative one at 206 ($\Delta\varepsilon$ −21.5) nm. The positive Cotton effects at 379 ($\Delta\varepsilon$ +1.9) and 240 ($\Delta\varepsilon$ +7.6) nm, and negative one at 208 ($\Delta\varepsilon$ −21.1) nm for **1** implied the absolute configuration at C-1′ to be *S*. Thus, the structure of papuabalanol A (**1**) was concluded to be a DHHDP ester of a dihydrochalcone glucoside.

Papuabalanol B (**2**), a yellow amorphous solid, $[\alpha]_D^{27}$ +24 (c=1.0, MeOH), had the molecular formula $C_{35}H_{30}O_{18}$ by HR-ESI-MS [m/z 737.1335, $(M-H)^-$, Δ −1.34 mmu], which was 16 mmu larger than that of **1**, corresponding to an oxygen atom. The UV and IR spectra of **2** were similar to those of **1**. Comparison of ^{1}H- and ^{13}C-NMR spectra of **2** with those of **1** suggested that **2** also contained a dihydrochalcone, a DHHDP group, and a glucose unit. The major difference of ^{1}H-NMR spectral data between **1** and **2** was the chemical shifts of a mono aromatic protons [δ_H 7.16—7.26 (5H, m); H-2‴—H-6‴], implying that **2** possessed substituted benzene ring. The absolute configuration of C-1′ was determined to be *S* by comparison of the CD spectral data with **1**. Thus, the structure of papuabalanol B (**2**) was concluded to be a dehydroxy derivative of papuabalanol A (**1**).

Compound **3** was identified as pinoresinol, which has been reported as (+) or (−) isomer from natural resources. The isolated **3** was elucidated as (−)-configuration by comparison of the optical rotation {**3**: $[\alpha]_D^{27}$ −88 (c=1.0, MeOH); −63 in the literature}.[7,12)]

Some hydrolysable tannins such as 1,2,6-tri-*O*-galloyl-β-D-glucose, 2,3-(*S*)-hexahydroxy diphenoyl (HHDP)-D-glucose, and pedunculagin inhibit tyrosinase activity in B16 melanoma cells[13,14)] as well as vasorelaxant effect on rat aorta.[15,16)] Preliminary experiments revealed that the ethyl acetate extract of *B. papuana* showed anti-tyrosinase activity using mushroom tyrosinase (inhibition rate, 78% at 100 μg/ml; 60% at 50 μg/ml). Papuabalanol B (**2**) showed inhibition of tyrosinase dose-dependently (IC_{50} 23.3 μM), but papuabalanol A (**1**) and pinoresinol (**3**) did not show any inhibition (IC_{50} >100 μM) as shown in Table 2. Tyrosinase is a key enzyme catalyzed production of melanin on melanogenesis. Papuabalanol B (**2**) decreased the melanin content in B16 melanoma cells in a dose-dependent manner. The cell viability was almost more than 80% at each concentration. Thus, papuabalanol B (**2**) reduced melanin production due to inhibition of tyrosinase (Table 2).

Papuabalanols A (**1**), B (**2**), and pinoresinol (**3**) were also tested vasorelaxant activity against phenylephrine (PE, 3×10^{-7} M)-induced contractions of thoracic rat aortic rings. When PE was applied to thoracic aortic rings with endothelium after achieving a maximal response, papuabalanol A (**1**) and pinoresinol (**3**) showed vasorelaxant activity at 100 μM, whereas papuabalanol B (**2**) did not exhibit the activity (Fig. 2). The effects of papuabalanol A-induced vasorelaxant action was attenuated by endothelium removal or pretreated with an NO synthase inhibitor, N^G-monomethyl-L-arginine (L-NMMA, 10^{-4} M), suggesting that the action was attributed

Table 2. Inhibition of Tyrosinase and Anti-melanogenesis Activity of **1**—**3**

	Anti-tyrosinase activity (%)			Anti-melanogenesis activity (%)		
	50 μM	25 μM	12.5 μM	100 μM	50 μM	25 μM
1	N.A.[a)]	N.A.[a)]	N.A.[a)]	N.D.[b)]	N.D.[b)]	N.D.[b)]
2	79	59	33	65	45	40
3	N.A.[a)]	N.A.[a)]	N.A.[a)]	N.D.[b)]	N.D.[b)]	N.D.[b)]
Kojic acid	84	55	31			
Arbutin				N.D.[b)]	32%	20%

a) N.A., not active at 50 μM. *b*) N.D., not determined.

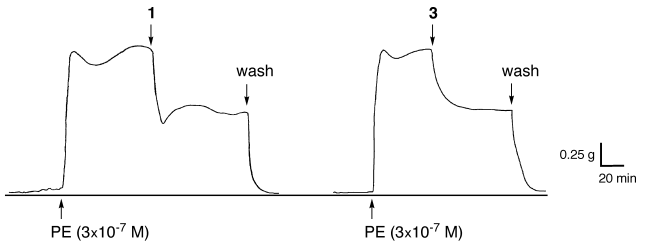


Fig. 2. Typical Recording of the Vasorelaxation Effects of **1** and **3** (Each 1×10^{-4} M) on the Rat Aortic Rings Precontracted with 3×10^{-7} M PE

to the endothelial cells to release nitric oxide (NO).

Experimental

General Experimental Procedures Optical rotations were measured on a JASCO DIP-1000 automatic digital polarimeter. UV spectra were obtained on an Ultrospec 2100 pro spectrophotometer, CD spectra were measured on a JASCO J-820 spectropolarimeter, and IR spectra were recorded on a JASCO FT/IR-4100 spectrophotometer. ^{1}H and 2D NMR spectra were recorded on a JEOL ECA600 and Bruker AV 400 spectrometers, and chemical shifts were referenced to the residual acetone-d_6 (δ_H 2.04 and δ_C 29.8). Standard pulse sequences were employed for the 2D NMR experiments. ^{1}H–^{1}H COSY spectrum was measured with spectral widths of both dimensions of 4800 Hz, and 32 scans with two dummy scans were accumulated into 1K data points for each of 256 t_1 increments. For HSQC spectra in the phase sensitive mode and HMBC spectra, a total of 256 increments of 1K data points were collected. For HMBC spectra with Z-axis PFG, a 50 ms delay time was used for long-range C–H coupling. Zero-filling to 1K for F_1 and multiplication with squared cosine-bell windows shifted in both dimensions were performed prior to 2D Fourier transformation. High-resolution ESI-MS were obtained on a LTQ Orbitrap XL (Thermo Scientific).

Plant Material A voucher specimen of *Balanophora papuana* was identified by Dr. Noramly Muslim, UKM, Malaysia and a voucher specimen was deposited at the herbarium of UKM, Malaysia.

Extraction and Isolation The fresh tubers of aerial part of *Balanophora papuana* (300 g) were extracted with ethyl acetate (3×500 ml, 3 d) at room temperature. After filtration and removal the solvent by evaporation *in vacuo*, a residue (31.2 g) was obtained. A part of the ethyl acetate extracts (1.82 g) was applied to a ODS column (Column A: 33×180 mm) and eluted with H_2O/MeOH gradient system (1 : 1 and 3 : 7) and MeOH to afford 6 fractions. A fraction (Fr. 2) of column A eluted with H_2O/MeOH (1 : 1) was further purified with an ODS HPLC (YMC-Pack ProC18, 10×250 mm; eluted with H_2O/acetonitrile (70 : 30); flow rate, 2.0 ml/min; UV detection at 254 nm) to afford ferulaldehyde (0.7 mg, t_R 19 min) and (−)-pinoresinol (15.8 mg, t_R 28 min). A fraction (Fr. 3) of column A eluted with H_2O/MeOH (1 : 1) was further purified with an ODS HPLC (Mightysil RP-18, 20×250 mm; eluted with H_2O/acetonitrile (65 : 35); flow rate, 5.0 ml/min; UV detection at 254 nm) to afford papuabalanol A (**1**: 13.6 mg, t_R 36 min). A fraction (Fr. 4) of column A eluted with H_2O/MeOH (3 : 7) was separated with a Sephadex LH-20 column (23×500 mm, eluted with MeOH), and the second fraction was further purified with an ODS HPLC (YMC-Pack ProC18, 10×250 mm; eluted with H_2O/acetonitrile (68 : 32); flow rate, 2.0 ml/min; UV detection at 254 nm) to afford papuabalanol B (**2**: 7.8 mg, t_R 30 min).

Papuabalanol A (**1**): Yellow amorphous solid; $[\alpha]_D^{27}$ +39 (c=1.0, MeOH); UV (MeOH) λ_{max} (log ε) 280 (5.4), 222 (5.6); CD (MeOH) λ_{max} ($\Delta\varepsilon$) 379 (+1.9), 240 (+7.6), 208 (−21.1); IR (film) ν_{max} 3375, 1716, and 1627 cm^{-1}; ^{1}H- and ^{13}C-NMR data (Table 1); ESI-MS m/z 753 (M−H)$^-$; HR-ESI-TOF-MS m/z 753.1280 [(M−H)$^-$, Calcd for $C_{35}H_{29}O_{19}$, 753.1298, Δ −1.75 mmu].

Papuabalanol B (**2**): Yellow amorphous solid; $[\alpha]_D^{27}$ +24 (c=1.0, MeOH); UV (MeOH) λ_{max} (log ε) 280 (5.2), 221 (5.5); CD (MeOH) λ_{max} ($\Delta\varepsilon$) 370 (+1.5), 240 (+6.7), 206 (−19.1); IR (film) ν_{max} 3401, 1723, 1709, and 1626 cm^{-1}; ^{1}H- and ^{13}C-NMR data (Table 1); ESI-MS m/z 737 (M−H)$^-$; HR-ESI-TOF-MS m/z 737.1335 [(M−H)$^-$, Calcd for $C_{35}H_{29}O_{18}$, 737.1348, Δ −1.34 mmu].

Acid Hydrolysis of 1 and 2 A solution of papuabalanol A (**1**: 1.0 mg) in 2 N HCl was heated at 100 °C for 2.5 h. The reaction mixture was evaporated *in vacuo*. The hydrolysate was dissolved in H_2O, subsequently to HPLC analysis (Capcell Pak NH_2 UG80, 4.6×250 mm; eluted with H_2O/acetonitrile (15 : 85); flow rate, 1.0 ml/min) with optical rotation detector. The hydrolysate was shown to be D-glucose by HPLC retention time (t_R 9.5 min), and sign (positive) of the optical rotation. Papuabalanol B (**2**) was also investigated in the same manner, and the sugar unit was identified as D-glucose by HPLC analysis.

Anti-melanogenesis Assay B16 cells were cultured in DMEM medim supplemented with 10% FBS and penicillin/streptmycin. B16 cells at 5000 cells in 100 μl per well were seeded onto 96-well microtiter plate, and were preincubated for 24 h at 37 °C in a humidified atmosphere containing 5% CO_2. The cells were cultured in the medium containing 3-isobutyl-1-methylxanthine (IBMX) (100 μM) with or without the test sample of different concentrations for 48 h, and then the medium were replaced the same condition fresh medium, further incubation for 48 h. The cells were dissolved in 50 μl of 1 N NaOH, and incubated at 90 °C for 1 h. Relative melanin content was determined spectrophotometrically by absorbance at 400 nm. Arbutin was used as a positive control.

Cell Viability Assay The cell viability was determined by 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) assay. Fifteen microliters of MTT solution (5 mg/ml) was added into each well of the cultured medium. After further 2 h incubation, the medium was removed, and then 50 μl of DMSO were added to resolve the formazan crystals. The optical density measurements were made using a microplate reader equipped with a two wavelengths system at 550 nm and 700 nm. In each experiment, three replicates were prepared for each sample. The ratio of the living cells was determined on the basis of the difference of the absorbance between those of samples and controls.

Tyrosinase Activity Assay Tyrosinase activity was spectrophotometrically determined as L-tyrosine oxidase activity of mushroom tyrosinase with same modifications. Briefly, 500 μl of 0.1 M phosphate buffer (pH 6.8) with or without different concentrations of test samples, 300 μl of 2.5 mM L-tyrosine were mixed in an eppentube. Two hundred microliters of the mixtures were transferred to 96-well microtiter plate. The absorbance at 475 nm was measured with microplate reader as a blank. Then, 50 μl of 200 units/ml tyrosinase was added to each well. After incubation at 37 °C for 15 min, the amount of dopachrome produced in the reaction mixture was determined spectrophotometrically at 475 nm on a microplate reader. The tyrosinase activity of each test sample was calculated as follow: % inhibition=100−$[(A-B)/C]\times100$ where A is the OD_{475} with enzyme and test sample; B the OD_{475} with test sample, but without enzyme; C the OD_{475} with enzyme, but without test sample. Kojic acid was used as a positive control.

Vasodilation Assay A male Wistar rat weighting 260 g was sacrificed by bleeding from carotid arteries under anesthesia. A section of the thoracic aorta between the aortic arch and the diaphragm was removed and placed in oxygenated, modified Krebs–Henseleit solution (KHS: 118.0 mM NaCl, 4.7 mM KCl, 25.0 mM $NaHCO_3$, 1.8 mM $CaCl_2$, 1.2 mM NaH_2PO_4, 1.2 mM

$MgSO_4$, and 11.0 mM glucose). The aorta was cleaned of loosely adhering fat and connective tissue and cut into ring preparations 3 mm in length. The tissue was placed in a well-oxygenated (95% O_2, 5% CO_2) bath of 5 ml of KHS solution at 37 °C with one end connected to a tissue holder and the other to a force-displacement transducer (Nihon Kohden, TB-611T). The tissue was equilibrated for 60 min under a resting tension of 1.0 g. During this time the KHS in the tissue bath was replaced every 20 min.

After equilibration, each aortic ring was contracted by treatment with 3×10^{-7} M phenylephrine (PE). The presence of functional endothelial cells was confirmed by demonstrating relaxation to 10^{-5} M acetylcholine (ACh), and aortic ring in which 80% relaxation occurred was regarded as tissue with endothelium. When the PE-induced contraction reached a plateau, each sample was added.

The animal experimental studies were conducted in accordance with the Guiding Principles for the Care and Use of Laboratory Animals, Hoshi University, and under the supervision of the Committee on Animal Research of Hoshi University, which is accredited by the Ministry of Education, Culture, Sports, Science and Technology of Japan.

Acknowledgments This work was partly supported by a Grant-in-Aid for Scientific Research from the Ministry of Education, Culture, Sports, Science and Technology of Japan, and a grant from the Open Research Center Project.

References and Notes

1) Trakulsomboon S., Kummalue T., Jiratchariyakul W., *J. Med. Assoc. Thai.*, **89**, 1466—1477 (2006).
2) Panthama N., Kanokmedhakul S., Kanokmedhakul K., *Chem. Pharm. Bull.*, **57**, 1352—1355 (2009).
3) Wang W., Zeng S. F., Yang C. R., Zhang Y. J., *Helv. Chim. Acta*, **92**, 1817—1822 (2009).
4) Jiang Z. H., Wen X. Y., Tanaka T., Wu S. Y., Liu Z., Iwata H., Hirose Y., Wu S., Kouno I., *J. Nat. Prod.*, **71**, 719—723 (2008).
5) Wang K. J., Zhang Y. J., Yang C. R., *Chem. Biodiver.*, **3**, 1317—1324 (2006).
6) Jiang Z. H., Takana T., Iwata H., Sakamoto S., Hirose Y., Kouno I., *Chem. Pharm. Bull.*, **53**, 339—341 (2005).
7) Moon S. S., Rahman A. A., Kim J. Y., Kee S. H., *Bioorg. Med. Chem.*, **16**, 7264—7269 (2008).
8) Tanaka T., Yamasaki K., Kohda H., Tanaka O., Mahato S. B., *Planta Med.*, **4**, 81—83 (1980).
9) Tanaka T., Fujisaka H., Nonaka G., Nishioka I., *Chem. Pharm. Bull.*, **40**, 2937—2944 (1992).
10) Okuda T., Yoshida T., Hatano T., *J. Chem. Soc. Perkin Trans. 1*, 9—14 (1982).
11) Okuda T., Yoshida T., Hatano T., Koga T., Toh N., Kuriyama K., *Tetrahedron Lett.*, **23**, 3941—3944 (1982).
12) Ishii H., Ishikawa, T., Mihara M., Akaike M., *Yakugaku Zasshi*, **103**, 279—293 (1983).
13) Ratan K. C., Zoia L., Germain P., *Cosmetics & Toiletries*, **122**, 73—74, 76, 78, 80 (2007).
14) Cho S. M., Kwon Y. M., Lee J. H., Lee M. W., *Nat. Prod. Sci.*, **8**, 183—185 (2002).
15) Legssyer A., Ziyyat A., Mekhfi H., Bnouham M., Herrenknecht C., Roumy V., Fourneau C., Laurens A., Hoerter J., Fischmeister R., *Phytother. Res.*, **8**, 889—894 (2004).
16) Andriambeloson E., Magnier C., Haan-Archipoff G., Lobstein A., Anton R., Beretz A., Stoclet J. C., Andriantsitohaina R., *J. Nutr.*, **128**, 2324—2333 (1998).