New Phenolic Constituents from *Balanophora polyandra* with Radical-Scavenging Activity

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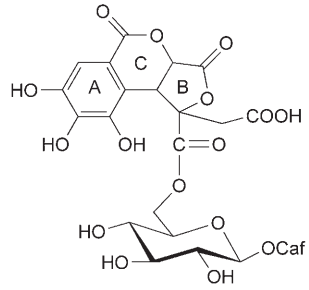
The 80% acetone extract of *Balanophora polyandra* GRIFF. (Balanophoraceae) was found to exhibit high radical-scavenging activity (SC_{50} = 14.48 μg/ml) towards 1,1-diphenyl-2-picrylhydrazyl (DPPH) radicals. Further chemical investigation led the isolation of two new hydrolysable tannins, balapolyphorins A (**1**) and B (**2**), together with 20 known phenolic compounds (**3**–**22**). Their structures were established by detailed spectroscopic analysis, and the radical-scavenging properties of all isolated compounds were determined by DPPH assay.

Introduction. – *Balanophora polyandra* GRIFF. (Balanophoraceae) is a parasitic plant mainly distributed in Southwest China, India, Vietnam, Thailand, and Nepal. The whole plant acts as an antipyretic, antidote, haemostatic, and haematic tonic, and has been used as a folk medicine for the treatment of gonorrhea, syphilis, wounds, and the bleeding of the alimentary tract by the local people in China [1]. So far, some hydrolysable tannins with galloyl, caffeoyl, and 'hexahydroxydiphenoyl' (HHDP) groups were found in the genus *Balanophora* [2][3]. However, no phytochemical study has been reported with this plant.

During our search for naturally occurring antioxidants from medicinal plants [4][5], preliminary experiments showed that *B. polyandra* contains significant amounts of polyphenolic compounds with considerable radical-scavenging activity in DPPH (= 1,1-diphenyl-2-picrylhydrazyl)-radical assay. Further bioassay-guided chemical investigation of the extract of *B. polyandra* led to the isolation of two new hydrolysable tannins, balapolyphorins A (**1**) and B (**2**), together with 20 known phenolic compounds, **3**–**22**. Herein, we report the structure determination of the new tannins as well as the radical-scavenging activities of **1**–**22**.

Results and Discussion. – 1. *Isolation and Structure Elucidation*. The 80% aqueous acetone extract of the fresh whole plant of *B. polyandra* exhibited obvious radical-scavenging activity (SC_{50} = 14.48 μg/ml) in DPPH assay. The crude extract was fractionated on *Diaion HP20SS* and further chromatographed on *Sephadex LH-20*, *CHP20P* (*MCI*), and *Chromatorex ODS* gel to afford balapolyphorins A (**1**) and B (**2**), together with 20 known phenolic compounds, including hydrolysable tannins **3**–**14**, lignan glucosides **15**–**17**, and simple aromatic compounds and glucosides **18**–**22**. The



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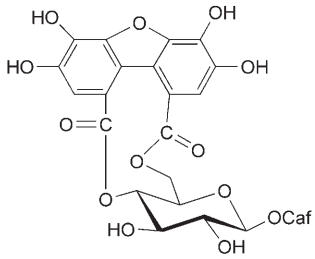

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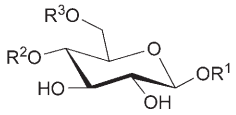

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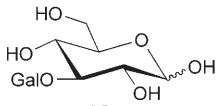
3 $R^1 = Caf$, $R^2 = R^3 = Gal$



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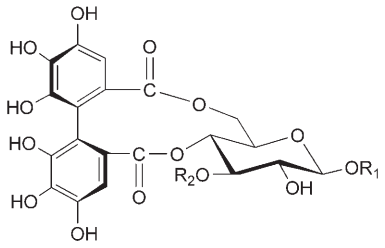

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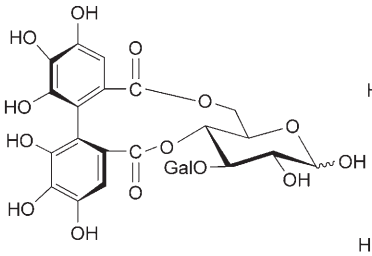

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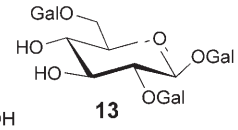

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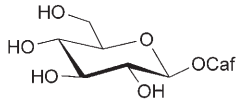

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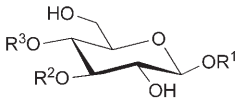

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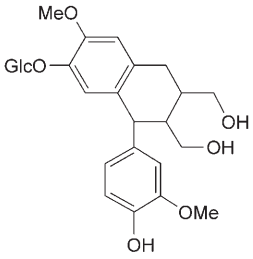
9 $R^1 = R^2 = Gal$, $R^3 = H$
10 $R^1 = R^2 = R^3 = Gal$
11 $R^1 = Gal$, $R^2 = Caf$, $R^3 = H$



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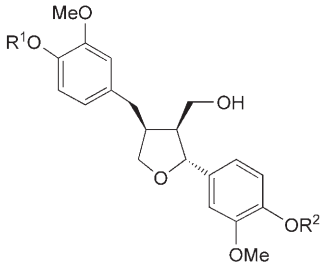

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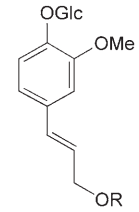
17 $R^1 = Glc$, $R^2 = H$



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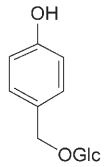

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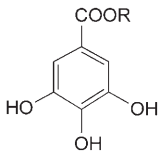
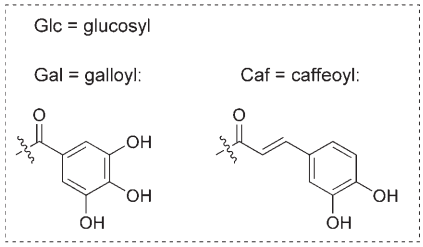


21 R = H
22 R = Me



known compounds[1]) were identified as 1-*O*-[(*E*)-caffeoyl]-4,6-di-*O*-galloyl-β-D-glucopyranose (**3**) [3], 1-*O*-[(*E*)-caffeoyl]-4,6-[1,1′-(3,3′,4,4′-tetrahydroxydibenzofurandicarboxyl)]-β-D-glucopyranose (**4**) [6], 1,3-di-*O*-galloyl-4,6-[(*S*)-hexahydroxydiphenoyl]-β-D-glucopyranose (**5**) [7], 1-*O*-galloyl-4,6-[(*S*)-hexahydroxydiphenoyl]-β-D-glucopyranose (**6**) [8], 3-*O*-galloyl-4,6-[(*S*)-hexahydroxydiphenoyl]-β-D-glucopyranose (**7**) [9], 1-*O*-galloyl-β-D-glucopyranose (**8**) [10], 1,3-di-*O*-galloyl-β-D-glucopyranose (**9**) [10], 1,3,4-tri-*O*-galloyl-β-D-glucopyranose (**10**) [11], 3-*O*-[(*E*)-caffeoyl]-1-*O*-galloyl-β-D-glucopyranose (**11**), 3-*O*-galloyl-β-D-glucopyranose (**12**), 1,2,6-tri-*O*-galloyl-β-D-glucopyranose (**13**) [12], 1-*O*-[(*E*)-caffeoyl]-β-D-glucopyranose (**14**) [2], isolariciresinol-4-*O*-β-D-glucoside (**15**) [13], lariciresinol-4-*O*-β-D-glucoside (**16**) [14], lariciresinol-4′-*O*-β-D-glucoside (**17**) [15], coniferin (**18**) [16], 9-methylconiferin (**19**) [17], 4-hydroxybenzyl-β-D-glucoside (**20**) [18], gallic acid (**21**), and methyl gallate (**22**). The known compounds were identified by TLC comparison with authentic samples and by comparison of their spectroscopic data with those reported in the literature.

Balapolyphorin A (**1**) was obtained as a brown, amorphous powder. The molecular formula $C_{29}H_{26}O_{19}$ was derived by negative HR-FAB-MS (*m/z* 677.0986 $[M-H]^-$) in combination with ^{13}C-NMR (DEPT) spectroscopy. On the basis of IR, and 1D- and 2D-NMR data (*Table 1*), as well as by comparison with the spectroscopic data of 1-*O*-[(*E*)-caffeoyl]-6-*O*-galloyl-β-D-glucopyranose [2], the structure of **1** was established as 1-*O*-[(*E*)-caffeoyl]-6-*O*-balapolyphoroyl-β-D-glucopyranose (=6-*O*-{[1-(carboxymethyl)-3,3a,5,9b-tetrahydro-7,8,9-trihydroxy-3,5-dioxo-1*H*-furo[3,4-*c*]isochromen-1-yl]carbonyl}-1-*O*-[(2*E*)-3-(3,4-dihydroxyphenyl)prop-2-enoyl]-β-D-glucopyranose).

The IR spectrum of **1** exhibited absorptions at 3431 (OH), 1774 (γ-lactone), 1708 (C=O), and 1625 cm^{-1} (C=C). The ^{1}H- and ^{13}C-NMR (DEPT) spectra of **1** were similar to those of 1-*O*-[(*E*)-caffeoyl]-6-*O*-galloyl-β-D-glucopyranose [2], with signals due to a caffeoyl group [δ(H) 7.05 (*d*, *J* = 1.9, H−C(2′)), 6.76 (*d*, *J* = 8.2, H−C(5′)), 6.92 (*dd*, *J* = 1.9, 8.2, H−C(6′)), 7.52 (*d*, *J* = 15.9, H−C(7′)), 6.20 (*d*, *J* = 15.9 Hz, H−C(8′))] and a 1,6-diacylated glucopyranosyl moiety. The *J* value of 8.1 Hz for the anomeric H-atom indicated β-configuration of the glucose moiety. However, instead of a 6-*O*-galloyl group, compound **1** had a different acyl group at C(6) of the glucose moiety. The sequential assignment of H- and C-atoms in this acyl group was made with the help of 2D-NMR experiments.

In the HMBC spectrum of **1** (*Fig. 1*), correlations of H−C(3‴) (δ(H) 7.06) with C(1‴) (δ(C) 117.6), C(2‴) (δ(C) 122.9), C(5‴) (δ(C) 135.3), and C(6‴) (δ(C) 147.8) suggested the presence of a pentasubstituted aromatic moiety (ring *A*). The HMBC correlations between H−C(2″) (δ(H) 4.79) with C(1″) (δ(C) 178.4), C(3″) (δ(C) 53.1), and C(4″) (δ(C) 90.8), and of H−C(3″) (δ(H) 4.90) with C(1″) (δ(C) 178.4), indicated a five-membered lactone (ring *B*), as further confirmed by the IR absorbance at 1774 cm^{-1}. The HMBC correlations of H−C(2″) (δ(H) 4.79) with C(2‴) (δ(C) 122.9) and C(7‴) (δ(C) 167.1), of H−C(3″) (δ(H) 4.90) with C(2‴) (δ(C) 122.9) and C(6‴) (δ(C) 147.8), and of H−C(3‴) (δ(H) 7.06) with C(7‴) (δ(C) 167.1) indicated a six-membered lactone (ring *C*). The signals at δ(C) 41.5 (C(5″)) and 167.1 (C(7″)) were both linked to C(4″) (δ(C) 90.8), on the basis of HMBC long-range couplings of H−C(5″) (δ(H) 2.95) with C(4″) (δ(C) 90.8), C(6″) (δ(C) 178.4), and C(7″) (δ(C)

[1]) Only the semisystematic or trivial names reported in the literature are given.

Table 1. *^{1}H- and ^{13}C-NMR Data of* **1** *and* **2**. At 500/125 MHz, resp., in CD_3OD; δ in ppm, J in Hz. Arbitrary atom numbering.

Position	**1**		**2**	
	δ(H)	δ(C)	δ(H)	δ(C)
Glc:				
1	5.52 (*d*, *J*=8.1)	95.3	5.70 (*d*, *J*=8.2)	95.7
2	3.43 (*dd*, *J*=8.3, 8.7)	73.4	3.60 (*dd*, *J*=8.5, 9.0)	74.2
3	3.76 (br. *s*)	75.7	3.82 (*dd*, *J*=8.3, 9.3)	75.8
4	3.47–3.50 (*m*)	70.8	5.21 (*dd*, *J*=9.6, 9.7)	72.0
5	3.50–3.54 (*m*)	76.8	4.04–4.08 (*m*)	74.4
6	4.83 (*d*, *J*=10.8), 4.38[a])	63.7	4.22 (*dd*, *J*=4.9, 12.5), 4.43 (*dd*, *J*=2.0, 12.5)	63.7
Caffeoyl:				
1′		127.5		127.6
2′	7.05 (*d*, *J*=1.9)	115.7	7.11 (*d*, *J*=2.0)	115.4
3′		145.9		146.8
4′		149.1		149.9
5′	6.76 (*d*, *J*=8.2)	116.9	6.78 (*d*, *J*=8.2)	116.5
6′	6.92 (*dd*, *J*=1.9, 8.2)	123.8	6.98 (*dd*, *J*=2.0, 8.2)	123.3
7′	7.52 (*d*, *J*=15.9)	148.6	7.68 (*d*, *J*=15.9)	148.6
8′	6.20 (*d*, *J*=15.9)	114.1	6.31 (*d*, *J*=15.9)	114.2
9′		168.1		167.5
Acyl:				
1″, 1‴		178.4, 117.6		121.1, 121.2
2″, 2‴	4.79 (br. *s*)	85.2, 122.9	6.99, 7.07 (2*s*)	110.4, 110.5
3″, 3‴	4.90 (br. *s*), 7.06 (*s*)	53.1, 113.1		146.4, 146.5
4″, 4‴		90.8, 146.8		139.9, 139.9
5″, 5‴	2.95 (*s*)	41.5, 135.3		146.4, 146.5
6″, 6‴		178.4, 147.8	6.99, 7.07 (2*s*)	110.4, 110.5
7″, 7‴		167.1, 167.1		167.6, 168.0

[a]) Overlapping with water signal.

167.1), as well as of H–C (3″) with C(7″) (δ(C) 167.1). Therefore, the acyl group at C(6) was established (see *Fig. 1*) and named balapolyphoroyl.

From the HMBC spectrum of **1**, the correlations of the anomeric resonance at δ(H) 5.52 with C(9′) at δ(C) 168.1, and of H–C(6) at δ(H) 4.38 and 4.83 with C(7″) at δ(C) 167.1, established the locations of the caffeoyl and balapolyphoroyl groups at C(1) and C(6) of the glucose moiety, respectively. From these data, the structure of balapolyphorin A (**1**) was unequivocally determined.

Balapolyphorin B (**2**) was obtained as a pale-brown, amorphous powder. The molecular formula was found to be $C_{29}H_{26}O_{17}$, as determined by HR-FAB-MS (*m*/*z* 645.1111 $[M-H]^-$). The structure of **2** was elucidated on the basis of spectroscopic evidence as 1,6-di-*O*-galloyl-4-*O*-(*E*)-caffeoyl-β-D-glucopyranose (=4-*O*-[(2*E*)-3-(3,4-dihydroxyphenyl)prop-2-enoyl]-1,6-bis-*O*-[(3,4,5-trihydroxyphenyl)carbonyl]-β-D-glucopyranose).

The ^{1}H- and ^{13}C-NMR (DEPT) spectra of **2** (*Table 1*) showed the presence of a β-D-glucopyranosyl moiety [δ(H) 5.70 (*d*, *J*=8.2, H–C(1)), δ(C) 95.7 (C(1))], two

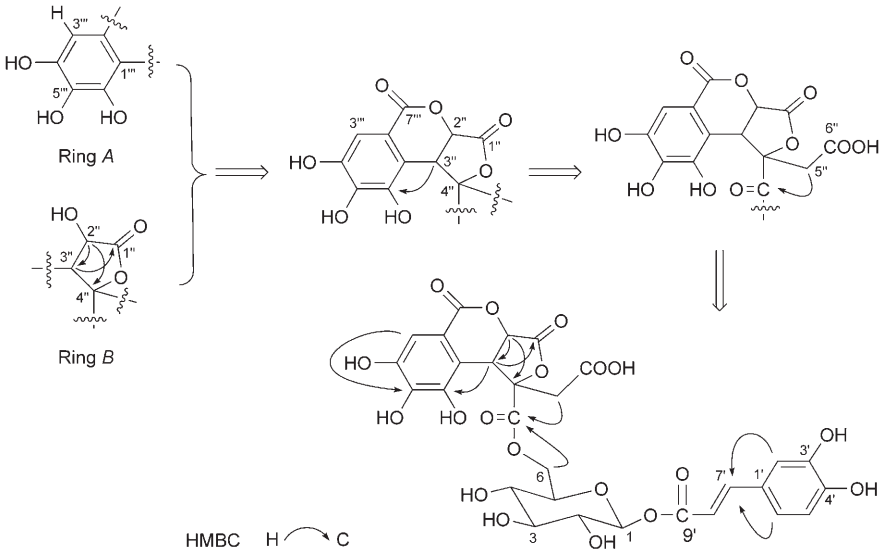


Fig. 1. *Key HMBC correlations for* **1**

galloyl residues [δ(H) 6.99, 7.07 (2*s*, H−C(2″,6″,2‴,6‴))], and one caffeoyl group [δ(H) 7.11 (*d*, J=2.0, H−C(2′)), 6.78 (*d*, J=8.2, H−C(5′)), 6.98 (*dd*, J=2.0, 8.2, H−C(5′)), 7.68 (*d*, J=15.9, H−C(7′)), 6.31 (*d*, J=15.9 Hz, H−C(8′))]. In the HMBC spectrum of **2** (*Fig. 2*), correlations were observed between the anomeric resonance at δ(H) 5.70 and the C=O resonance at δ(C) 167.6 (C(7″)) of one galloyl group, of CH_2(6) at δ(H) 4.22/4.43 with C(7‴) (δ(C) 168.0) of the second galloyl group, and of H−C(4) (δ(H) 5.21) with C(9′) (δ(C) 167.5) of the caffeoyl group. This suggested that the latter was linked at C(4) of glucose, whereas the two former groups were attached at C(1) and C(6), respectively. On the basis of the above evidences, the structure of **2** was unequivocally determined.

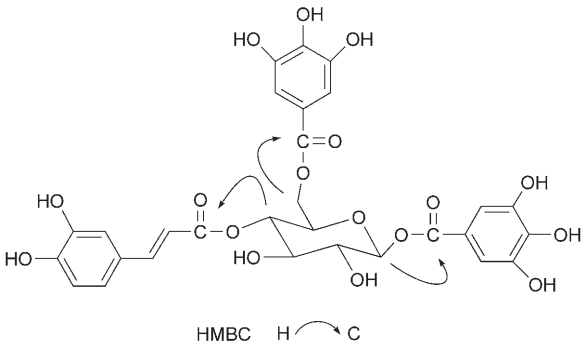


Fig. 2. *Key HMBC correlations for* **2**

2. *Radical-Scavenging Activity.* Compounds **1**–**22** were subjected to radical-scavenging-activity tests using the DPPH assay. The results are collected in *Table 2*. As can be seen, most of the isolated compounds showed radical-scavenging activity. Among the isolated constituents from *B. polyandra*, the hydrolysable tannins **1**–**14** displayed especially high activities, with SC_{50} values in the range of 8.4–46.4 μM, the activities decreasing in the order **5** > **6** > **13** > **7** > **4** > **10** > **9** > **3** > **2** > **8** > **12** > **11** > **1** > **14**. This result is in accord with the known trend that hydrolysable tannins with several adjacent OH groups (as in galloyl, pyrogalloyl, or catechol groups) display high radical-scavenging activities in DPPH assays [19]. Both gallic acid (**21**) and its methyl ester **22** also exhibited high activities. Gallic acid (**21**), widely found in plants, was reported to act as a pro-oxidant in inducing DNA fragmentation and apoptosis of several tumor cells [20][21], and compound **22** was reported to have a protective effect against H_2O_2-induced oxidative stress and cell DNA damage [22]. Finally, the lignans **15**–**17** and the simple aromatic glucosides **18** and **19** displayed only weak activities in the DPPH assay. In summary, these results seem to indicate that phenolic compounds play an important role for the radical-scavenging activity of this plant.

Table 2. *DPPH-Radical-Scavenging Activities of* **1**–**22**. SC_{50} is the compound concentration required for 50% reduction of DPPH radicals. All values are given as means ± SD ($n = 3$). For details, see *Exper. Part*.

Compound	SC_{50} [μM]	Sample	SC_{50} [μM]
Ascorbic acid[a])	30.8 ± 0.3	**12**	34.4 ± 0.9
1	41.5 ± 0.4	**13**	13.6 ± 0.3
2	25.4 ± 0.3	**14**	46.4 ± 0.2
3	20.8 ± 0.3	**15**	202 ± 3
4	16.4 ± 0.2	**16**	293 ± 4
5	8.4 ± 0.2	**17**	252 ± 7
6	13.0 ± 0.3	**18**	392 ± 8
7	15.3 ± 0.3	**19**	201 ± 5
8	31.9 ± 0.5	**20**	68.3 ± 0.9
9	19.7 ± 0.2	**21**	12.1 ± 0.2
10	16.7 ± 0.4	**22**	19.3 ± 0.2
11	37.4 ± 0.6		

[a]) Positive control.

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Experimental Part

General. UV Spectra were recorded on a *Shimadzu UV-2401PC* apparatus; in λ_{max} (log ε). Optical rotations were measured on a *JASCO-20* polarimeter. IR Spectra were recorded in KBr cells on a *Bio-Rad FTS-135* spectrophotometer; in cm^{-1}. NMR Spectra were recorded in (D_6)acetone and CD_3OD on a *Bruker DRX-500* instrument at 500 (^1H) and 125 MHz (^{13}C) at 25°; δ in ppm rel. to Me_4Si, J in Hz. Mass spectra were recorded on a *VG AutoSpeC-3000* mass spectrometer; in m/z (rel. %). Column chromatography (CC) was performed on *Diaion HP20SS* (*Mitsubishi Chemical Co.*), *CHP20P* gel

(75–150 μm; *Mitsubishi Chemical Co.*), *Sephadex LH-20* gel (25–100 μm; *Pharmacia Fine Chemical Co., Ltd.*), *Chromatorex-ODS* gel (100–200 mesh; *Fuji Silysia Chemical Co., Ltd.*), and *Toyopearl HW-40F* (37–70 μm; *Tosoh Co.*). TLC was carried on silica-gel-precoated plates (*Qingdao Haiyang Chemical Co., Ltd.*) eluting with benzene/ethyl formate/formic acid 3 : 6 : 1; spots were detected by spraying with solns. of $FeCl_3$ and 10% H_2SO_4.

Plant Material. The whole, fresh plant of *Balanophora polyandra* GRIFF. was collected from Wenshan County, Yunnan Province, China, in November 2003, and identified by Prof. *Su-Gong Wu*, Kunming Institute of Botany, Chinese Academy of Sciences. A voucher specimen (No. KY031102) was deposited at the State Key Laboratory of Phytochemistry and Plant Resources in West China, Kunming Institute of Botany, Chinese Academy of Sciences.

Extraction and Isolation. The whole, fresh plant of *B. polyandra* (3.8 kg) was cut into small pieces and extracted with 80% aq. acetone (3×10 l, 24 h each) at r.t. The combined extracts were concentrated under reduced pressure to afford a residue (620 g) that showed an SC_{50} value as 14.48 μg/ml on DPPH assay. Accordingly, further isolation was carried out. Thus, the crude extract (300 g) was purified by CC (*Diaion HP 20SS*, 10×100 cm column, step gradient of H_2O/MeOH $1:0 \rightarrow 0:1$, then H_2O/acetone 1 : 1) to afford nine fractions (*Fr. 1–9*; 500 ml each), each of which was purified by repeated CC on *Sephadex LH-20*, *CHP20P* gel, and *Chromatorex-ODS* gel, eluting each time with a step gradient of H_2O/MeOH $1:0 \rightarrow 0:1$. From *Fr. 2* (45 g), compounds **1** (14 mg), **5** (25 mg), **8** (22 mg), **12** (80 mg), **21** (80 mg), **22** (22 mg), **16** (14 mg), **18** (100 mg), **19** (60 mg), and **20** (10 mg) were obtained. From *Fr. 3* (18 g), compounds **6** (30 mg), **7** (30 mg), and **9** (25 mg) were isolated. *Fr. 4* (12 g) afforded **3** (25 mg) and **10** (20 mg). *Fr. 5* (16 g) gave **11** (10 mg), **13** (16 mg), **14** (22 mg), **15** (22 mg), and **17** (22 mg). And *Fr. 6* (9 g) provided **2** (18 mg) and **4** (22 mg).

Balapolyphorin A (=*6*-O-*{[1-(Carboxymethyl)-3,3a,5,9b-tetrahydro-7,8,9-trihydroxy-3,5-dioxo-1*H-*furo[3,4-c]isochromen-1-yl]carbonyl}-1*-O-*[(2*E*)-3-(3,4-dihydroxyphenyl)prop-2-enoyl]-β-*D-*glucopyranose*; **1**). Brown, amorphous powder. UV (MeOH): 219 (4.41), 286 (4.11), 316 (4.09). $[\alpha]_D^{21} = -6.85$ ($c =$ 0.3, H_2O). IR (KBr): 3431, 1774, 1708, 1625, 1394, 1227. ^{1}H- and ^{13}C-NMR: see *Table 1*. FAB-MS (neg.): 677 ($[M-H]^-$). HR-FAB-MS: 677.0986 ($[M-H]^-$, $C_{29}H_{25}O_{19}^-$; calc. 677.0990).

Balapolyphorin B (=*4*-O-*[(2*E*)-3-(3,4-Dihydroxyphenyl)prop-2-enoyl]-1,6-bis*-O-*[(3,4,5-trihydroxyphenyl)carbonyl]-β-*D-*glucopyranose*; **2**). Pale-brown, amorphous powder. UV (MeOH): 204 (3.94), 250 (3.20) 255 (3.20), 261 (3.05). $[\alpha]_D^{21} = +55.02$ ($c = 0.5$, MeOH). IR (KBr): 3422, 1707, 1611, 1344, 1323, 1225, 1063, 1034. ^{1}H- and ^{13}C-NMR: see *Table 1*. FAB-MS (neg.): 645 ($[M-H]^-$). HR-FAB-MS: 645.1111 ($[M-H]^-$, $C_{29}H_{25}O_{17}^-$; calc. 645.1091).

Radical-Scavenging Assay. DPPH was purchased from *Aldrich*. The radical-scavenging assays were performed with an *Emax* precision microplate reader as described elsewhere [18], ascorbic acid being used as positive control. Briefly, the reaction mixtures containing an ethanolic soln. of 200 μM DPPH (100 μl) and test compound (prepared in twofold serial dilutions in 100 μl EtOH at concentrations of 2–1000 μg/ml) were placed in a 96-well microplate and incubated at 37° for 30 min. After incubation, the UV/VIS absorbance A was read at 517 nm, and the mean value from three duplicated readings was taken. The scavenging activity was determined by the following equation: percent activity $= [A_{control} - A_{sample}]/A_{control} \times 100$. The SC_{50} value was obtained through extrapolation from linear regression analysis; it denotes the concentration of sample required to scavenge 50% of the DPPH radicals.

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