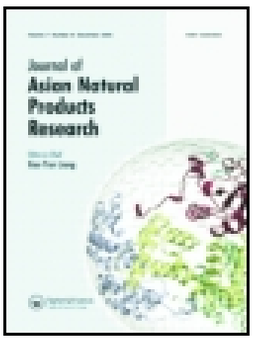

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New phenolic glycosides from *Polygonum cuspidatum*

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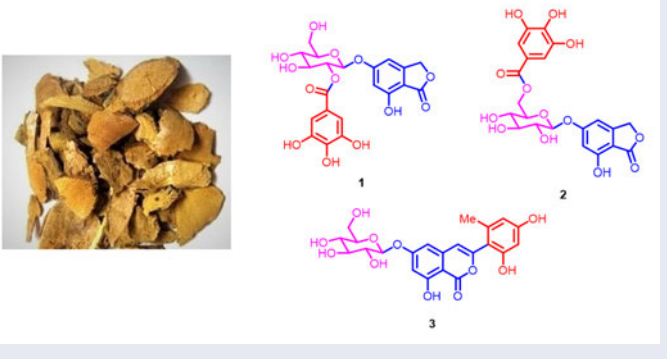
ABSTRACT

Two new isobenzofuranone derivatives, polyphthaliside A (**1**) and polyphthaliside B (**2**), and a new isocoumarin derivative, polyisocoumarin (**3**), were isolated from *Polygonum cuspidatum*. Their structures were elucidated by detailed spectroscopic analysis and chemical methods. The cytotoxicity activity and PTP1B inhibitory activity of compounds 1–3 were estimated and none of them exhibited activities at a concentration of 10 μM.



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Polygonum cuspidatum; isobenzofuranone; isocoumarin; cytotoxicity activity; PTP1B

1. Introduction

Polygonum cuspidatum is the dried rhizome of Polygonaceae and has been widely reported for its various traditional biological activities, including suppurative dermatitis, gonorrhea, chronic bronchitis, jaundice, amenorrhea, hypertension, hyperlipemia, and menopausal symptoms [1, 2]. Previous investigations have revealed that *P. cuspidatum* contained a variety of phytochemical constituents such as flavonoids [3], anthraquinones [4], stilbenes [1], and other phenols [5]. In the course of searching for active components from this plant, two new isobenzofuranone derivatives and a new isocoumarin derivative were isolated and named polyphthaliside A (**1**),

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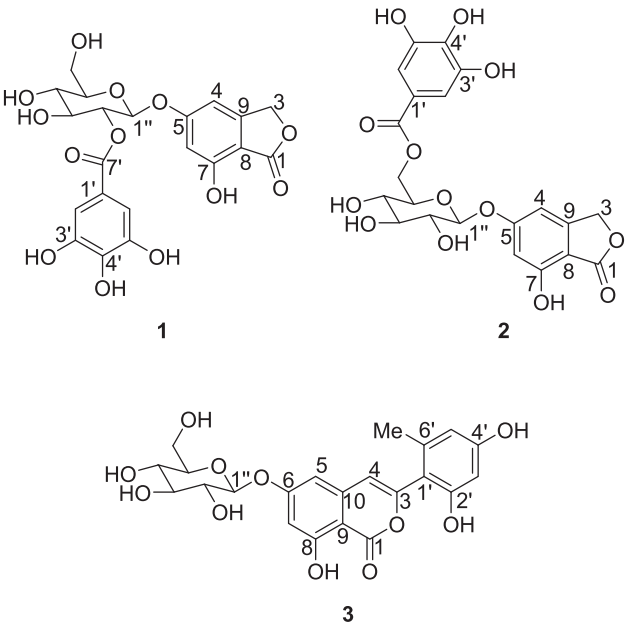

Figure 1. Chemical structures of compounds **1–3**.

polyphthaliside B (**2**), and polyisocoumarin (**3**) (Figure 1). Additionally, compounds **1–3** were evaluated for the cytotoxicity activity and the PTP1B inhibition.

2. Results and discussion

Compound **1** was obtained as a white powder. The IR spectrum of **1** showed the presence of hydroxyl groups (3384 cm^{-1}), carbonyl groups (1718 cm^{-1}), and aromatic rings (1614, 1535, 1451 cm^{-1}). A molecular formula of $C_{21}H_{20}O_{13}$ ($\Omega = 12$) was deduced on the basis of HR-ESI-MS at *m/z* 479.0834 $[M–H]^-$. The ^1H NMR spectrum of **1** (Table 1) displayed the signals for aromatic protons at δ_H 6.95 (2H, s, H-2′,6′), 6.59 (1H, s, H-4) and 6.35 (1H, s, H-6), an anomeric proton at δ_H 5.27 (1H, d, $J = 8.5$ Hz, H-1″), and two oxygenated methylene protons at δ_H 5.16 (1H, d, $J = 16.5$ Hz, H-3a) and 5.13 (1H, d, $J = 16.5$ Hz, H-3b). The ^{13}C NMR spectrum of **1** (Table 1) showed 21 carbon signals including seven carbons of a galloyl group at δ_C 119.3 (C-1′), 108.8 (C-2′,6′), 145.5 (C-3′,5′), 138.6 (C-4′), 164.9 (C-7′), six carbons of a benzene ring at δ_C 100.2 (C-4), 163.1 (C-5), 103.5 (C-6), 158.1 (C-7), 105.8 (C-8), 151.4 (C-9), six carbons of a glycosyl moiety at δ_C 98.0 (C-1″), 73.4 (C-2″), 74.0 (C-3″), 69.6 (C-4″), 77.3 (C-5″) and 60.3 (C-6″), an ester carbonyl carbon at δ_C 168.2 (C-1), and an oxygenated methylene carbon at δ_C 68.5 (C-3) combining with 2D NMR spectra. In HMBC spectrum (Figure 2), the cross-peaks between H-3 (δ_H 5.16 and 5.13)/C-1 (δ_C 168.2) demonstrated that the ester carbonyl carbon (C-1) was linked to the C-3 position of the methylene by oxygen atom. Meanwhile, the methylene was directly attached at C-9 of the benzene ring based on the correlations of H-3 with C-4, C-8 and C-9 in the HMBC experiment. Therefore, compound **1** was concluded to contain an isobenzofuranone group and the NMR spectral data due to the

Table 1. ^{1}H (500M) and ^{13}C NMR (125M) spectroscopic data of compounds **1**–**3** (DMSO-d_6).

	1		2		3	
No.	δ_C	δ_H	δ_C	δ_H	δ_C	δ_H
1	168.2		168.4		166.5	
2						
3	68.5	5.16, *d* (16.5) 5.13, *d* (16.5)	68.0	5.05, *d* (16.0) 4.92, *d* (16.0)	152.1	
4	100.2	6.59, s	98.4	6.50, s	109.3	6.66, s
5	163.1		163.6		104.1	6.75, *d* (2.0)
6	103.5	6.35, s	104.3	6.42, s	164.8	
7	158.1		155.6		102.8	6.63, *d* (2.0)
8	105.8		105.6		162.8	11.06, s (OH)
9	151.4		151.2		100.8	
10					140.1	
1′	119.3		119.1		111.8	
2′	108.8	6.95, s	108.5	6.96, s	157.6	9.57, s (OH)
3′	145.5		145.7		100.7	6.25, *d* (1.5)
4′	138.6		138.7		159.7	9.57, s (OH)
5′	145.5		145.7		108.8	6.19, *d* (1.5)
6′	108.8	6.95, s	108.5	6.96, s	139.6	
7′	164.9		165.7		20.3	2.13, s
1″	98.0	5.27, *d* (8.5)	99.9	4.95, *d* (8.5)	100.4	5.04, *d* (7.0)
2″	73.4	4.95, *t* (8.5)	73.1	3.28–3.30, m	73.6	3.27–3.29, m
3″	74.0	3.59–3.61, m	76.3	3.32–3.34, m	77.7	3.39–3.41, m
4″	69.6	3.34–3.36, m	69.8	3.28–3.10, m	70.0	3.18–3.20, m
5″	77.3	3.49–3.51, m	73.9	3.70, *t* (8.5)	77.0	3.29–3.31, m
6″	60.3	3.56–3.58, m 3.74, *d* (11.0)	63.5	4.17, dd (11.0, 6.5) 4.49, *d* (11.0)	61.0	3.48–3.50, m 3.69–3.71, m

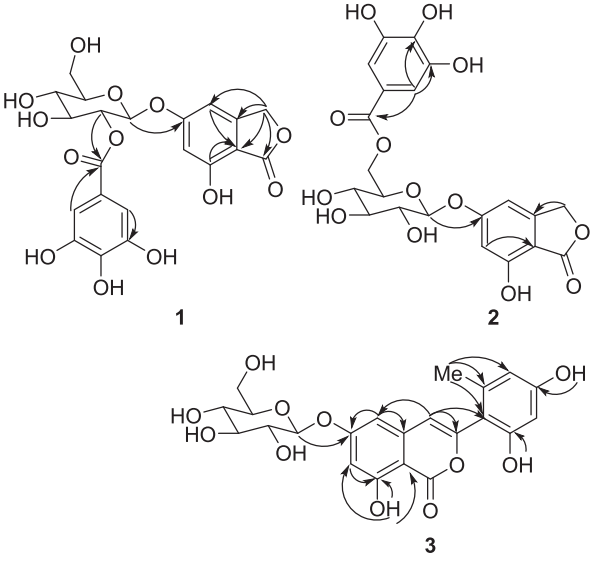

Figure 2. Key HMBC (H→C) correlations of compounds **1**–**3**.

group were in accord with those reported for 5,7-dihydroxy-1(3*H*)-isobenzofuranone [6]. Additionally, the glycosyl moiety was assigned to be *β*-form by the coupling constant of the anomeric proton signal ($J = 8.5$ Hz) and the glycosyl moiety was proved to be D-glucose based on the GC analysis by acid hydrolysis of **1**. Above all the information indicated that the structure of **1** consisted of a glucosyl moiety, a galloyl group

and a 5,7-dihydroxy-1(3*H*)-isobenzofuranone moiety. Furthermore, the HMBC correlations between H-1″/C-5, and H-2″/C-7′ confirmed that the glucosyl moiety and the galloyl group were located at C-5 of the isobenzofuranone, and C-2″ of the glucosyl, respectively. Thus, compound **1** was defined and named polyphthaliside A.

Compound **2** was also isolated as a white powder. Its molecular formula of $C_{21}H_{20}O_{13}$ was determined by HR-ESI-MS. The IR spectrum showed the presence of hydroxyl, carbonyl and aromatic groups. The ^{1}H NMR spectral data (Table 1) showed aromatic proton signals at δ_H 6.96 (2H, s, H-2′,6′), 6.50 (1H, s, H-4), and 6.42 (1H, s, H-6), an anomeric proton signal at δ_H 4.95 (1H, d, $J = 8.5$ Hz, H-1″), and two methylene proton signals at δ_H 5.05 (1H, d, $J = 16.0$ Hz, H-3a) and 4.92 (1H, d, $J = 16.0$ Hz, H-3b). The ^{13}C NMR spectrum of **2** showed 21 carbon signals (Table 1) comprising seven carbons of a galloyl group, six carbons of a glycosyl moiety, and eight carbons of 5,7-dihydroxy-1(3*H*)-isobenzofuranone coupling with 2D NMR spectra. These observations suggested that compound **2** was still an isobenzofuranone derivative. The ^{13}C NMR spectrum of **2** was similar to the corresponding signals of compound **1** except of chemical shift of C-6″ in the glucosyl group. This indicated that the galloyl group was linked to the C-6″ position based on the information that the chemical shift was moved from δ_C 60.3 (C-6″) in compound **1** to δ_C 63.5 (C-6″) in compound **2**. Additionally, *β*-D-pyranoglucose was confirmed by the acid hydrolysis and located at C-5 by the correlation of H-1″/C-5 in HMBC experiment (Figure 2). Finally, compound **2** was characterized as depicted and named polyphthaliside B.

Compound **3** was obtained as a white powder. The IR spectrum of **3** showed the presence of hydroxyl groups (3305 cm^{-1}), carbonyl groups (1667 cm^{-1}), benzene ring (1509, 1465 cm^{-1}) and methyl (2932, 1347 cm^{-1}). **3** possessed a molecular formula of $C_{22}H_{22}O_{11}$ on the basis of HR-ESI-MS at *m/z* 463.1233 $[M+H]^+$. The ^{1}H NMR spectrum (Table 1) showed three phenolic hydroxyl protons at δ_H 11.06 (1H, s, OH-8) and 9.57 (2H, s, OH-2′,4′), two sets of *meta*-coupled aromatic protons at δ_H 6.75 (1H, d, $J = 2.0$ Hz, H-5) and 6.63 (1H, d, $J = 2.0$ Hz, H-7), and δ_H 6.25 (1H, d, $J = 1.5$ Hz, H-3′) and 6.19 (1H, d, $J = 1.5$ Hz, H-5′), an olefin bond proton at δ_H 6.66 (1H, s, H-4), an anomeric proton at δ_H 5.04 (d, $J = 7.0$ Hz, H-1″), and a methyl proton at δ_H 2.13 (3H, s). Coupling with 2D NMR, the ^{13}C NMR spectrum (Table 1) displayed a set of saccharide carbon signals at δ_C 100.4 (C-1″), 73.6 (C-2″), 77.7 (C-3″), 70.0 (C-4″), 77.0 (C-5″) and 61.0 (C-6″). The saccharide moiety was assigned to be *β*-form by the large coupling constant of the anomeric proton signal and the ^{13}C NMR data. Furthermore, cellulose hydrolysis of **3** yielded D-glucose based on the GC analysis, which suggested that there was a *β*-D-glucopyrancose in compound **3**. The ^{13}C NMR and 2D NMR data of **3** further established a methyl at δ_C 20.3 (C-7′), and a tetrasubstituted phenyl at δ_C 111.8 (C-1′), 157.6 (C-2′), 100.7 (C-3′), 159.7 (C-4′), 108.8 (C-5′) and 139.6 (C-6′). In addition, the tetrasubstituted phenyl was concluded to be 2′,4′-dihydroxy-6′-methylphenyl coupling with the correlations of OH-2′ (δ_H 9.57)/C-2′, OH-4′ (δ_H 9.57)/C-4′, and H-CH_3/C-1′, C-5′, C-6′ in the HMBC experiment (Figure 2). Except for 13 carbons of a glucosyl and 2′,4′-dihydroxy-6′-methylphenyl, the residual 9 carbon signals of **3** showed close similarities to those of 6,8-dihydroxy-3-(2-hydroxypropyl)-isocoumarin [7], which confirmed that compound **3** has a 3,6,8-trisubstituted isocoumarin group. Meanwhile, the HMBC correlations of

H-4/C-3, C-5 and C-1′ indicated that the tetrasubstituted phenyl was located at C-3 of isocoumarin group. Additionally, the glucosyl was linked to C-6 by the correlation of H-1″/C-6 observed in the HMBC experiment. Consequently, compound **3** was established and named polyisocoumarin.

Few literatures were reported about isobenzofuranone and isocoumarin from *P. cuspidatum*. Compounds **1** and **2** were the kind of isobenzofuranone, and **3** was the kind of isocoumarin, as determined by detailed spectroscopic means (NMR, and MS *et al.*). These compounds rich the diversity of these ingredients in *P. cuspidatum*. A modern study revealed that its extract exhibited antioxidaion, anti-tyrosinase, immune stimulation, anticancer and antidiabetic activities [8,9]. Accordingly, all the isolated compounds were evaluated for their cytotoxicity activity and PTP1B inhibitory effects, but the results showed that these compounds exhibited no obvious activity.

3. Experimental

3.1. General experimental procedures

The optical rotations were measured on a Jasco P-2000 polarimeter (Jasco, Easton, Japan). IR spectra were recorded on a Nicolet 5700 spectrometer (Thermo Scientific, Waltham, USA). UV spectra were obtained on a JASCO V-650 spectrophotometer (Jasco, Easton, Japan). ^{1}H NMR (500 MHz), ^{13}C NMR (125 MHz), HSQC, and HMBC spectra were run on an INOVA-500 spectrometer (Bruker-Biospin, Billerica, USA). High-resolution electrospray ionization mass spectrometry (HRESIMS) was performed on an Agilent 1100 series LC/MSD ion trap mass spectrometer (Agilent Technologies, Waldbronn, Germany). Column chromatography was performed with Macroporous resin (Diaion HP-20, Mitsubishi Chemical Corp., Tokyo, Japan), Rp-18 (50 μm; YMC, Kyoto, Japan), and Sephadex LH-20 (Pharmacia Fine Chemicals, Uppsala, Sweden). Preparative HPLC was carried out on a Shimadzu LC-6AD instrument with a SPD-20A detector (Shimadzu, Tokyo, Japan), using a YMC-Pack ODS-A column (250 × 20 mm, 5 μm).

3.2. Plant material

The rhizome of *Polygonum cuspidatum* was purchased from Beijing Pu Sheng Lin Pharmaceutical Co., Ltd. of China, in Feb 2010. The plant material was identified by associate professor L. Ma (Institute of Materia Medica, Peking Union Medical College and Chinese Academy of Medical Sciences). A voucher specimen (ID number: ID-S-2593) was deposited in the Herbarium of the Department of Medicinal Plants, Institute of Materia Medica, Chinese Academy of Medical Sciences, and Peking Union Medical College, Beijing, China.

3.3. Extraction and isolation

Powdered *P. cuspidatum* (20 kg) was extracted with 80% EtOH under reflux (3 × 2 h). The EtOH extract was concentrated under reduced pressure to give a residue (4.2 kg), which was suspended in H_2O (4 L) and partitioned with, consecutively, petroleum

ether (PE) (3 × 4 L), EtOAc (3 × 4 L), and n-BuOH (3 × 4 L). After evaporation of the n-BuOH solvent under reduced pressure, the extract (1.4 kg) was suspended in H_2O (2 L) and subjected to column chromatography over macroporous resin, eluting successively with H_2O, 30% EtOH, 50% EtOH, 70% EtOH, and 95% EtOH (30 L each). The 30% EtOH was removed under reduced pressure and the fraction (86.4 g) was subjected to chromatography over Sephadex LH-20 with H_2O–MeOH in gradient as the mobile phase to yield 25 fractions (Fr.A–Fr.Y) on the basis of HPLC-DAD analysis.

Fr.G (0.2 g) was purified by preparative RP-HPLC using MeOH–H_2O (35:65, with a flow rate of 5.0 ml/min, 280 nm) as the mobile phase to yield **2** (4.0 mg, retention time: 36.7 min). Fr.H (0.3 g) was purified by preparative RP-HPLC using MeOH–H_2O (55:50, with a flow rate of 5.0 ml/min, 280 nm) as the mobile phase to yield **3** (30.0 mg, retention time: 38.7 min). Fr.I (2.0 g) was subjected to Sephadex LH-20 column and eluted with MeOH–H_2O (from 20:80 to 60:40) to afford 20 fractions (Fr.I-1–I-20). Fr.I-15 (0.3 g) was further purified using preparative RP-HPLC with MeOH–H_2O (20:80, with a flow rate of 5.0 ml/min, 280 nm) as the mobile phase to yield **1** (9.0 mg, retention time: 41.6 min).

3.3.1. Polyphthaliside A (1)

White powder; $[\alpha]_D^{20}$ −27.3 (*c* 0.02, H_2O); UV (MeOH) λ_{max}: 214, 252, 288 nm; IR ν_{max}: 3384, 1718, 1614, 1535, 1451 cm^{-1}; ^1H NMR (DMSO-d_6, 500 MHz) and ^{13}C NMR (DMSO-d_6, 125 MHz) spectral data see Table 1. HR-ESI-MS: *m/z* 479.0834 $[M-H]^-$ (calcd for $C_{21}H_{19}O_{13}$, 479.0831).

3.3.2. Polyphthaliside B (2)

White powder; $[\alpha]_D^{20}$ −23.3 (*c* 0.01, H_2O); UV (MeOH) λ_{max}: 214, 252, 288 nm; IR ν_{max}: 3397, 1723, 1614, 1506, 1452 cm^{-1}; ^1H NMR (DMSO-d_6, 500 MHz) and ^{13}C NMR (DMSO-d_6, 125 MHz) spectral data see Table 1.

3.3.3. Polyisocoumarin (3)

White powder; $[\alpha]_D^{20}$ −59.9 (*c* 0.05, H_2O); UV (MeOH) λ_{max}: 236, 256, 336 nm; IR ν_{max}: 3305, 2932, 1667, 1590, 1465, 1347 cm^{-1}; ^1H NMR (DMSO-d_6, 500 MHz) and ^{13}C NMR (DMSO-d_6, 125 MHz) spectral data see Table 1.

3.4. Acid hydrolysis of compounds

Compound **1** (2 mg) was dissolved in 1 mol/L HCl–dioxane (1:1, 3 ml) and maintained at 60 °C for 6 h. After drying *in vacuum*, the residue was partitioned in H_2O (3 ml) and extracted thrice with EtOAc (3 ml). The aqueous solution was evaporated *in vacuum* to obtain the monosaccharide residue. The configurational assignment of glucose was established by comparing the retention times of their chiral derivatives with those of standard substances, which were prepared using the identical procedure (D-glucose 20.56 min) [10]. The same operating procedure was used for compound **2**.

3.5. Cellulose hydrolysis of compound 3

A solution of **3** (2 mg) in 2 ml 0.1 M HOAc–NaOAc buffer (pH = 4.5) was incubated at 40 °C with cellulose (2 mg) for 5 h. The reaction was monitored by HPLC-DAD analysis. After cooling, the reaction mixture was extracted with EtOAc (3 × 5 ml). The aqueous layer was evaporated under vacuum to furnish a crude sugar fraction.

Disclosure statement

No potential conflict of interest was reported by the authors.

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