Diverse Polyphenols from *Hypericum faberi*

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Abstract

Six new polyphenols with different isoprenylated xanthenes, isoprenylated acylphloroglucinols, and chromone architectures, hyperfaberols A–F (**1–6**), were isolated from the whole plants of *Hypericum faberi* along with seven other related known compounds. In which hyperfaberols A/B (**1/2**) and **12–13** were isoprenylated xanthenes, hyperfaberols C–E (**3–5**) and **8–11** were seven isoprenylated acylphloroglucinol derivatives, while **6–7** were two chromones. Their structures were elucidated by comprehensive analysis of their spectroscopic data as well as detailed comparison with the literature data. Compounds **1** and **11** showed cytotoxicities against the human esophageal cancer cell line (ECA-109) and the pancreatic tumor cell line (PANC-1) in vitro, respectively.

Graphical Abstract

Keywords *Hypericum faberi* · Isoprenylated xanthone · Isoprenylated acylphloroglucinol · Chromone · Cytotoxicity

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1 Introduction

The genus *Hypericum* (Hypericaceae Juss.) comprises nearly 500 species and is subdivided into 36 taxonomic sections [1]. The plants of this genus have been proved to be rich sources of prenylated phenolic metabolites with diverse phloroglucinols, xanthenes, and flavonoids structures as well as valuable bioactivities such as antidepressant, antibacterial, and antiproliferative activities [2–4]. Our group has been engaged in the systematic studies of isoprenylated polyphenols from *Hypericum* species for more than ten years, and has discovered a series of fascinating chemical structures with intriguing biological activities [5–15].

Hypericum faberi R. Keller is distributed in the south and west of China [16]. Detailed literature research shows that it has never been phytochemical studied before. To further explore the new and bioactive natural polyphenols from *Hypericum* species, *H. faberi* was selected to carry out a phytochemical study and six new polyphenols, hyperfaberols A–F (**1**–**6**), together with additional seven known related derivatives 5,7-dihydroxy-2-isopropylchromon (**7**) [17], madeleinal A (**8**) [18], empetrifranzinans A/B (**9/10**) [18], otogirin (**11**) [19], dulxanthone D (**12**) [20], and toxyloxanthone B (**13**) [21] were isolated. It's noteworthy that these isolates can be divided to three group based on their structural characters: isoprenylated xanthenes (**1**–**2** and **12**–**13**), isoprenylated acylphloroglucinols (**3**–**5** and **8**–**11**), and chromones (**6**–**7**). In the bioactive assay, compounds **1** and **11** showed cytotoxicities against the human esophageal cancer cell line (ECA-109) and the pancreatic tumor cell line (PANC-1) in vitro, respectively. Herein, we report the results of the isolates from the whole plant of *H. faberi* and their biological evaluation.

2 Results and Discussion

Hyperfaberol A (**1**) was obtained as a yellow amorphous powder. The HRESIMS data showed a deprotonated molecular ion at m/z 461.1979 $[M-H]^-$, indicating a molecular formula of $C_{28}H_{30}O_6$ (calcd for $C_{28}H_{29}O_6$, 461.1970). The IR spectrum showed absorption bands of hydroxy (3423 cm^{-1}) and conjugated carbonyl (1634 cm^{-1}) functionalities. The ^1H NMR spectrum showed a hydroxy group (δ_H 13.24), two aromatic protons (δ_H 6.14 and 6.73), two protons of a terminal double bond (δ_H 4.37, 4.48, 1H each, s), and five methyls (δ_H 1.34–1.64, s) (Table 1). The ^{13}C and DEPT NMR data showed 28 carbon signals which were sorted by HSQC techniques as five methyls, three methylenes (including one terminal double bond, δ_C 111.0 and 147.2), six methines, and 14 quaternary carbons. The typical thirteen signals for a carbonyl (δ_C 181.6) and two *penta*-substituted phenyl units (δ_C 162.5, 160.3, 154.0, 153.5, 152.4, 138.2, 119.5, 106.0, 104.5, 102.4, 102.0, 97.1) can be easily distinguished in the ^{13}C NMR, which indicated a xanthone skeleton of **1** as hinted by the UV absorption bands at 203, 267 and 333 [22, 23]. In the HMBC spectrum, the correlations from 1-HO to C-1, C-2, C-9, and C-9a; from H-2 to C-1, C-3, C-4, C-9, and C-9a; from H-5 to C-6, C-7, C-8a, C-9, and C-10a, and from H₂-11 to C-3, C-4, and C-4a confirmed the xanthone framework (Fig. 2).

Carefully analysis of the 1D NMR spectra indicated the remaining 15 carbon signals (from C-11 to C-25) should assigned to three isoprenyl derived units. Two of which were deduced to form a lavandulyl moiety by the ^1H - ^1H COSY cross-peaks of H₂-11/H-12/H₂-13/H-14 together with the

Table 1 ^{13}C (150 MHz) and ^1H (600 MHz) NMR Data of **1** (in DMSO)

No.	δ_C (type)	δ_H (J in Hz)	No.	δ_C (type)	δ_H (J in Hz)
1	160.3 (C)		13	31.0 (CH ₂)	2.02, m
2	97.1 (CH)	6.14, s	14	123.0 (CH)	4.96, t (6.9)
3	162.5 (C)		15	130.9 (C)	
4	104.5 (C)		16	25.5 (CH ₃)	1.55, s
4a	154.0 (C)		17	17.6 (CH ₃)	1.45, s
10a	153.5 (C)		18	147.2 (C)	
5	102.4 (CH)	6.73, s	19	18.4 (CH ₃)	1.64, s
6	152.4 (C)		20	111.0 (CH ₂)	4.37, s
7	138.2 (C)				4.48, s
8	119.5 (C)		21	120.3 (CH)	7.82, d (10.2)
8a	106.0 (C)		22	132.6 (CH)	5.86, d (10.2)
9	181.6 (C)		23	75.0 (C)	
9a	102.0 (C)		24	26.6 (CH ₃)	1.34, s
11	26.4 (CH ₂)	2.65, m	25	26.6 (CH ₃)	1.34, s
12	46.9 (CH)	2.35, m	HO-1		13.24, s

HMBC correlations from H₂-20 to C-12, C-18 and C-19, and from H₃-16/H₃-17 to C-14 and C-15. The location of this lavandulyl moiety at C-4 was evidenced by the HMBC correlations of H-11 with C-3, C-4, and C-4a [24]. The third isoprenyl group was elucidated to form a characteristic pyran ring between C-7 and C-8 as revealed by the HMBC correlations from H-21 to C-7, C-8, C-8a, and C-23, and from H₃-24/H₃-25 to C-7, C-22, and C-23. Consequently, the structure of **1**, hyperfaberol A, was established as shown (Fig. 1).

Hyperfaberol B (**2**), a yellow amorphous powder, had the molecular formula $C_{19}H_{16}O_6$ as deduced from its HRESIMS m/z 339.0881 $[M-H]^-$ (calcd for 339.0874) and ^{13}C NMR data. The IR spectrum showed absorption bands of hydroxy (3370 cm^{-1}) and conjugated carbonyl (1664 cm^{-1}). The ^1H NMR revealed the presence of one hydroxy (δ_H 13.15, s), three aromatic protons [δ_H 6.43 (1H, s), 6.97 (1H, d, $J=8.8\text{ Hz}$), and 7.90 (1H, d, $J=8.8\text{ Hz}$)], two protons of a terminal double bond (δ_H 4.94, 5.09, 1H each, s), one methyl (δ_H 1.76, 3H, s), and one methoxy group (δ_H 4.09, 3H, s) (Table 2). The ^{13}C NMR spectrum exhibited 19 signals, including 15 sp^2 carbons [one carbonyl, 12 aromatic carbons, and a terminal double bond signals (δ_C 113.0 and 143.3)] and four sp^3 carbons (one methyl, one methoxy, one methylene, and one oxygenated methine). Side-by-side analysis of the ^1H and ^{13}C NMR spectra indicated that **2** were closely similar to the known xanthone, 2,3-dihydro-4-hydroxy-9-methoxy-2-(1-methylethenyl)-6*H*-furo[3,2-*b*]xanthen-5-one [25]. The only difference was that the aromatic proton (H-3) in the latter was replaced by a hydroxy group in **2**, which can be confirmed by the downfield chemical shift of 154.3 (C-3), the obvious HMBC correlations

Fig. 1 Structures of 1–13

Table 2 ^{13}C (150 MHz) and ^1H (600 MHz) NMR Data of **2** (in CDCl_3)

No.	δ_{C} (type)	δ_{H} (J in Hz)	No.	δ_{C} (type)	δ_{H} (J in Hz)
1	122.0 (CH)	7.90, d (8.8)	9	180.4 (C)	
2	112.5 (CH)	6.97, d (8.8)	9a	115.1 (C)	
3	154.3 (C)		11	62.2 (CH_3)	4.09, s
4	133.8 (C)		12	30.7 (CH_2)	3.02, dd (15.4, 7.4)
4a	149.7 (C)				3.37, dd (15.4, 9.7)
10a	157.9 (C)		13	88.6 (CH)	5.34, dd (9.4, 7.7)
5	89.5 (CH)	6.43, s	14	143.3 (C)	
6	167.3 (C)		15	17.2 (CH_3)	1.76, s
7	108.0 (C)		16	113.0 (CH_2)	4.94, s
8	158.2 (C)				5.09, s
8a	103.6 (C)		HO-8		13.15, s

from the two *ortho*-coupled aromatic protons H-1/H-2 to C-3, from H-1 to C-9, C-9a, and C-4a, from H-2 to C-3, C-4, C-9, and C-9a, from H-5 to C-6, C-7, C-8a, C-9, and C-10a, from HO-8 to C-7, C-8, C-8a, and C-9, from H₂-12 to C-6, C-7, and C-8, from H₂-16 to C-13, C-14, and C-15, and the ^1H - ^1H COSY between H₂-12 and H-13. Thus, the structure of **2** was elucidated and named hyperfaberol B (Fig. 1).

Hyperfaberol C (**3**) was isolated as a yellow gum. The molecular formula was established as $\text{C}_{21}\text{H}_{32}\text{O}_6$ from its ^{13}C NMR (Table 3) and HRESIMS data (m/z 379.2136, $[\text{M}-\text{H}]^-$, calcd for 379.2126). The IR absorptions implied

hydroxy (3417 cm^{-1}) and carbonyl (1622 cm^{-1}) functionalities. Its ^1H NMR spectrum showed three hydroxy groups (δ_{H} 10.26, 10.51 and 14.14), an isopropyl group (δ_{H} 1.05, 6H, d, $J=6.7$ Hz; 3.89, sept., $J=6.7$ Hz), three singlet methyls (δ_{H} 0.94, 1.01, and 1.66), a methoxy group (δ_{H} 3.03), one olefinic proton (δ_{H} 5.11), and one aromatic proton (δ_{H} 5.97). The ^{13}C and DEPT NMR spectrum showed 21 carbon signals including 10 signals assignable to an isobutyryl (δ_{C} 209.5, C-7; 38.0, C-8; and 19.3, C-9/10) and a phloroglucinol core (δ_{C} 102.7, C-1; 163.8, C-2; 106.0, C-3; 162.2, C-4; 94.2, C-5; and 159.6, C-6), which indicated that **3** could be an acylphloroglucinol derivative. The location of the acyl group at C-1 was evidenced by the HMBC correlation of HO-2 with C-7 and further indicated the formation of intramolecular hydrogen bonding between the hydroxyl and the carbonyl group. In addition, the HMBC correlations from HO-2 to C-1, C-2, and C-3, from HO-4 to C-3, C-4, and C-5, and from HO-6 to C-1, C-5, and C-6 were all presented, which confirmed the phloroglucinol core furthermore. The remaining eleven signals was assigned to three methyls, one methoxy, three methylenes, two methines (including one sp^2 methine), and two quaternary carbons (including one sp^2 carbon). The ^1H - ^1H COSY correlations of H₂-11/H-12 and H₂-15/H₂-16/H-17, conjugated with the HMBC correlations from H₃-14 to C-12, C-13, and C-15, from H₃-19/H₃-20 to C-17 and C-18, and from H₃-21 to C-18, established the 6-hydroxy-7-methoxy-3,7-dimethyl-2-octenyl partial structure for the fifteen signals moiety (Fig. 2) [26]. Moreover, the HMBC correlations from H₂-11 to C-2, C-3 and

Table 3 ^{13}C (150 MHz) and ^1H (600 MHz) NMR Data of **3** and **4** (in DMSO)

No.	3		4	
	δ_{C} (type)	δ_{H} (J in Hz)	δ_{C} (type)	δ_{H} (J in Hz)
1	102.7 (C)		102.6 (C)	
2	163.8 (C)		163.8 (C)	
3	106.0 (C)		105.9 (C)	
4	162.2 (C)		162.2 (C)	
5	94.2 (CH)	5.97, s	94.2 (CH)	5.98, s
6	159.6 (C)		159.6 (C)	
7	209.5 (C)		209.5 (C)	
8	38.0 (CH)	3.89, sept. (6.7)	38.0 (CH)	3.89, sept. (6.7)
9	19.3 (CH ₃)	1.05, d (6.7)	19.3 (CH ₃)	1.05, d (6.7)
10	19.3 (CH ₃)	1.05, d (6.7)	19.3 (CH ₃)	1.05, d (6.7)
11	20.9 (CH ₂)	3.06, d (6.8)	20.9 (CH ₂)	3.07, dd (3.1, 6.4)
12	122.7 (CH)	5.11, t (6.8)	122.8 (CH)	5.09, t (6.7)
13	133.8 (C)		133.3 (C)	
14	16.1 (CH ₃)	1.66, s	16.1 (CH ₃)	1.66, s
15	36.4 (CH ₂)	1.82, m	35.2 (CH ₂)	1.82, m
16	29.2 (CH ₂)	1.12, m	33.4 (CH ₂)	1.42, m
17	74.4 (CH)	3.14, dd (10.3, 4.6)	73.5 (CH)	3.78, t (7.2)
18	76.8 (C)		148.2 (C)	
19	21.6 (CH ₃)	1.01, s	17.6 (CH ₃)	1.59, s
20	19.6 (CH ₃)	0.94, s	109.8 (CH ₂)	4.67, s
21	48.6 (CH ₃)	3.03, s		4.79, s
HO-2		14.14, s		14.13, s
HO-4		10.26, s		10.26, s
HO-6		10.51, s		10.52, s

C-4 established the attachment of the moiety at C-3. The NOE correlations of H₂-11/Me-14 and H₂-12/H₂-15 in the ROESY spectrum elucidated the 12*E*-configured double bond of the moiety. Thus, the structure of hyperfaberol C (**3**) was elucidated (Fig. 1).

Hyperfaberol D (**4**), was obtained as a yellow gum, the molecular formula, C₂₀H₂₈O₅, was established by HRESIMS data (m/z 347.1871 [M-H][−], calcd for 347.1864). Comparison of the 1D NMR data indicated that the structures of **4** and **3** were very similar to each other (Table 3). The difference lied in that compound **3** has one more methoxy group than **4**, meanwhile, the oxygenated quaternary carbon (δ_{C} 76.8, C-18) and Me-20 (δ_{C} 19.6) in **3** were also replaced by a terminal double bond (δ_{C} 148.2, C-18; and 109.8, C-20) in **4**, which could be confirmed by the ^1H - ^1H COSY cross-peaks of H₂-11/H-12 and H₂-15/H₂-16/H-17, and the HMBC correlations from H₃-14 to C-12, C-13, and C-15, from H₂-20 to C-17, C-18, and C-19, and from H₂-11 to C-2, C-3, and C-4. In the ROESY spectrum, an NOE cross-peak between Me-14 and H₂-11 was observed, indicating the *E* configuration of C-12/13 double bond of the moiety (Fig. 2). Thus, the structure of **4** was therefore established to be that show in Fig. 1.

Hyperfaberol E (**5**) gave the molecular formula of C₂₀H₂₈O₅ by the HRESIMS m/z 347.1876 [M-H][−] (calcd for 347.1864). Its structure was elucidated to possess similar acylphloroglucinol scaffold with that of empetrikathiforin by detailed analysis of its MS and 1D NMR data [27]. The only difference lies in that the *sec*-butyl group in empetrikathiforin was replaced by an isopropyl in **5** [δ_{H} 3.86 (1H, sept., J =6.7 Hz, H-8), 1.02 (3H each, d, J =6.7 Hz, H-9/H-10); δ_{C} 38.1, C-8; 19.3, C-9/10] (Table 4), which was confirmed by the ^1H - ^1H COSY cross-peaks of H-8/H₃-9/H₃-10 and the HMBC correlations of Me-9/Me-10 to C-7 and C-8 (Fig. 2).

Hyperfaberol F (**6**) was isolated as an amorphous powder. Its molecular formula of C₁₃H₁₄O₄ was assigned on the basis of its ^{13}C NMR data and the observed [M-H][−] ion at m/z 233.0823 (calcd for C₁₃H₁₃O₄, 233.0819). The IR absorptions implied the presence of hydroxy (3417 cm^{−1}) and conjugated carbonyl (1622 cm^{−1}) groups. The ^1H NMR revealed the presence of two aromatic protons at δ_{H} 6.14 (1H, d, J =1.6 Hz) and 5.97 (1H, d, J =1.6 Hz), and a singlet olefinic proton at δ_{H} 5.94 (1H, s), as well as a *sec*-butyl group at δ_{H} 2.49 (1H, m), 1.03 (3H, d, J =6.9 Hz), 1.38 and 1.50 (2H, each m), and 0.68 (3H, s). The ^{13}C NMR spectrum exhibited 13 signals, including nine sp² carbons (one

Fig. 2 Key HMBC, ^1H - ^1H COSY, and ROESY correlations of **1**, **3**, and **6**

Table 4 ^{13}C (150 MHz) and ^1H (600 MHz) NMR Data of **5** (in DMSO)

No.	δ_{C} (type)	δ_{H} (J in Hz)	No.	δ_{C} (type)	δ_{H} (J in Hz)
1	102.8 (C)		13	152.1 (C)	
2	164.1 (C)		14	108.1 (CH_2)	4.61, s
3	104.2 (C)				4.78, s
4	163.0 (C)		15	26.0 (CH_2)	2.03, m
5	94.5 (CH)	5.90, s	16	31.0 (CH_2)	2.02, m
6	160.1 (C)		17	124.5 (CH)	5.06, m
7	209.5 (C)		18	130.6 (C)	
8	38.1 (CH)	3.86, sept. (6.7)	19	25.5 (CH_3)	1.59, s
9	19.3 (CH_3)	1.02, d (6.7)	20	17.5 (CH_3)	1.52, s
10	19.3 (CH_3)	1.02, d (6.7)	HO-2		13.90, s
11	29.3 (CH_2)	2.66, dd (13.5, 5.3)2.53, m	HO-4		10.26, s
12	73.5 (CH)	4.14, t (6.3)	HO-6		10.78, s

Table 5 ^{13}C (150 MHz) and ^1H (600 MHz) NMR Data of **6** (in DMSO)

No.	δ_{C} (type)	δ_{H} (J in Hz)	No.	δ_{C} (type)	δ_{H} (J in Hz)
2	173.6 (C)		8	98.9 (CH)	5.97, d (1.6)
3	106.4 (CH)	5.94, s	8a	161.5 (C)	
4	181.7 (C)		9	39.4 (CH)	2.49, m
4a	103.4 (C)		10	17.5 (CH_3)	1.03, d (6.9)
5	157.9 (C)		11	26.9 (CH_2)	1.38, m
6	93.8 (CH)	6.14, d (1.6)			1.50, m
7	164.9 (C)		12	11.4 (CH_3)	0.68, s

carbonyl, six aromatic carbons, and two olefinic carbons) and four sp^3 carbons (two methyls, one methylene, and one methine) (Table 5). The nine downfield sp^2 signals indicated that **6** possessed a chromone skeleton, while the four signals

for sp^3 carbons relatively upfield confirmed the presence of the *sec*-butyl group observed in the ^1H NMR spectrum. The 1D NMR data of **6** was similar to those of **5**, 7-dihydroxy-2-isopropylchromon (**7**) [17], the difference lies in that the isopropyl in **7** was substituted by a *sec*-butyl group (δ_{C} 39.4, C-9; 17.5, C-10; 26.9, C-11; and 11.4, C-12) in **6**, which can be proved by the correlations from H-9 to C-2 in the HMBC spectrum, as well as the long linkage of H-9/ H_3 -10/ H_2 -11/ H_3 -12 in the ^1H - ^1H COSY spectrum (Fig. 2). Thus, the structure of **6** was assigned as shown.

Empetrifranzinan A/B (**9/10**) have been previously described from *Hypericum empetrifolium* [18]. However, the relative configurations of the two compounds were not given in previous literature, and which are demonstrated herein. In the ROESY spectrum of **9**, the NOE correlations of H-11/H-12a, H-12a/H-15b/H-17, and H-12a/ H_3 -14 suggested the β -orientation of H-11, Me-14, and H-17. The same relative configuration of **10** was also established as shown in Fig. 3.

The inhibitory activities of the isolates were examined against the five human tumor cell lines (ECA-109, PANC-1, BIU-87, and BEL-7402) with taxol as the positive control (IC_{50} values of 1.2, 3.5, 2.1 and 1.9 μM , respectively) [28]. Compound **1** showed cytotoxicity against the human esophageal cancer cell line (ECA-109) with an IC_{50} value of 12.8 μM , while compound **11** exhibited activity against the pancreatic tumor cell line (PANC-1) with an IC_{50} value of 12.0 μM . Additionally, other isolates showed no activities against the five human tumor cell lines with IC_{50} values > 30 μM .

3 Experimental

3.1 General Experimental Procedures

Optical rotations were measured on a JASCO P-1020 polarimeter. UV spectra were recorded on a Shimadzu

Fig. 3 Key NOESY correlations of **9** and **10**

UV-2401PC spectrometer. IR spectra were recorded on a Bruker FT-IR Tensor-27 infrared spectrophotometer with KBr disks. 1D and 2D NMR spectra were recorded on a Bruker DRX-600 spectrometer using TMS as an internal standard. The chemical shifts (δ) were expressed in ppm with reference to the solvent signals. ESIMS and HR-ESIMS analysis were carried out on Waters Xevo TQS and Agilent G6230 TOF mass spectrometers, respectively. Preparative and semi-preparative HPLC were performed on Waters 1525 HPLC (column: SunFire OBD- C_{18} , 19×250 mm) and Agilent 1100 HPLC (column: Zorbax SB- C_{18} , 9.4×250 mm), respectively. Silica gel (100–200 and 200–300 mesh, Qingdao Marine Chemical Co., Ltd., People's Republic of China), and MCI gel (75–150 μ m, Mitsubishi Chemical Corporation, Tokyo, Japan) were used for column chromatography. Fractions were monitored by TLC (GF 254, Qingdao Marine Chemical Co., Ltd.), and spots were visualized by heating silica gel plates immersed in H_2SO_4 in ethanol.

3.2 Plant Material

The whole plants of *H. faberi* were collected in Yiliang County, Zhaotong City, Yunnan Province, China. It was identified by Dr. Yong-Zeng Zhang in Kunming Institute of Botany. A voucher specimen (no. 201707H01) has been deposited at the Kunming Institute of Botany.

3.3 Extraction and Isolation

The dried whole plants of *H. faberi* (15.0 kg) were powdered and percolated with MeOH at room temperature and filtered. The filtrate was evaporated in vacuo to be concentrated. The crude extract (3.2 kg) was subjected to a silica gel column chromatography (CC) using elution of successive $CHCl_3$ and EtOAc to give a non-polar fraction (163.0 g) and a polar fraction (192 g). The $CHCl_3$ fraction was separated by an MCI-gel CC (MeOH- H_2O , 70–100%) to yield six fractions (Fr. 1–6, polarity from small to large). Fr. 3 (10.2 g) was separated by a Rp-18 column (49×460 mm, MeOH- H_2O , 80–100%) to obtain eleven subfractions (Fr. 3-1 to Fr. 3-11) on the basis of TLC analysis. Fr. 3-7 (226.1 mg) was fractionated by preparative HPLC (MeOH- H_2O , 88%) to afford Fr. 3-7-1, which was further purified by semipreparative HPLC (MeOH- H_2O , 85%) to give the **11** (5.6 mg). Fr. 3-8 (271.7 mg) was fractionated by preparative HPLC (MeOH- H_2O , 86%) to afford Fr. 3-8-1, which was further separated by semipreparative HPLC (MeOH- H_2O , 80%) to obtain compound **1** (4.7 mg). Fr. 3-10 (184.2 mg) was purified by preparative HPLC (MeOH- H_2O , 80%) to yield compound **9** (8.4 mg) and **10** (5.0 mg). Fr. 4 (11.5 g) was separated by a Rp-18 column (MeOH- H_2O , 70–100%)

to obtain thirteen subfractions (Fr. 4-1 to Fr. 4-13). Fr. 4-7 (394.6 mg) was fractionated by preparative HPLC (MeOH- H_2O , 93%) to afford Fr. 4-7-1, which was then purified by semipreparative HPLC (MeOH- H_2O , 90%) to afford the **2** (1.3 mg).

The EtOAc fraction (192 g) was separated by an MCI-gel CC (MeOH- H_2O , 45–90%) to obtain five fractions (Fr. E1–E5, polarity from small to large). Fr. E1 (25.1 g) was separated by silica gel CC (petroleum ether/EtOAc, from 400:1 to 0:1) to give eight subfractions, Fr. E1-1 to Fr. E1-8. Fr. E1-4 (603.1 mg) was purified by repeated preparative HPLC (MeOH/ H_2O : 80%) to yield the **3** (2.6 mg). Fr. E2 (11.7 g) was separated by silica gel CC (petroleum ether/EtOAc, from 50:1 to 0:1) to give eleven subfractions, Fr. E2-1 to Fr. E2-11. Fr. E2-3 (142.3 mg) was further purified by preparative HPLC (MeOH/ H_2O : 75%) to yield the **5** (1.8 mg). Fr. E2-4 (1.4352 g) was further isolated sequentially using Sephadex LH-20 (Acetone), preparative HPLC (MeOH/ H_2O : 70%) to yield the **12** (1.7 mg). Fr. E3 (10.5 g) was separated by silica gel CC (petroleum ether/EtOAc, from 25:1 to 0:1) to obtain ten subfractions, Fr. E3-1 to Fr. E3-10. Fr. E3-3 (533.5 mg), Fr. E3-4 (392.1 mg), and Fr. E3-6 (1.2 g) was separated by Sephadex LH-20 (Acetone), and purified by prep-HPLC (MeOH/ H_2O : 70%) to afford compounds **6** (1.8 mg), **7** (2.3 mg), **8** (2.1 mg), **13** (1.5 mg). Fr. E3-8 (562.7 mg) was separated by silica gel CC (petroleum ether/EtOAc, from 10:1 to 0:1) to give eight subfractions, Fr. E3-8-1 to Fr. E3-8-8. Fr. E3-8-2 (405.2 mg) was further subjected to a silica gel CC ($CDCl_3$ /MeOH, from 400:1 to 0:1) to give Fr. E3-8-2-1 to Fr. E3-8-2-8. Fr. E3-8-2-4 (62.4 mg) was further purified by semipreparative HPLC (MeOH/ H_2O : 70%) to yield the **4** (3.3 mg).

3.3.1 Hyperfaberol A (1)

Yellow amorphous powder; $[\alpha]_D^{25} +19$ (c 0.12, MeOH); UV (MeOH) λ_{max} (log ϵ): 385 (3.74), 333 (4.25), 267 (4.36), 245 (4.33), 203 (4.52) nm; IR (KBr) ν_{max} : 3423, 2968, 2925, 1634, 1574, 1454 cm^{-1} ; 1H and ^{13}C NMR data, see Table 1; ESIMS m/z 461 $[M-H]^-$; HR-ESIMS m/z 461.1979 $[M-H]^-$ (calcd for $C_{28}H_{29}O_6$, 461.1970).

3.3.2 Hyperfaberol B (2)

Yellow amorphous powder; $[\alpha]_D^{20} +6$ (c 0.13, MeOH); UV (MeOH) λ_{max} (log ϵ): 323 (4.4), 283 (4.02), 248 (4.66), 214 (4.40) nm; IR (KBr) ν_{max} : 3370, 3083, 2925, 2854, 2731, 1664, 1613, 1518, 1403, 1374, 1228, 1161, 1032 cm^{-1} ; 1H and ^{13}C NMR data, see Table 2; ESIMS m/z 339 $[M-H]^-$; HR-ESIMS m/z 339.0881 $[M-H]^-$ (calcd for $C_{19}H_{15}O_6$, 339.0874).

3.3.3 Hyperfaberol C (3)

Yellow gum; $[\alpha]_D^{20}$ –34 (*c* 0.12, MeOH); UV (MeOH) $\lambda_{\max}$ (log ϵ) 291 (4.16), 197 (4.31) nm; IR (KBr) $\nu_{\max}$ 3417, 2975, 2932, 2874, 1215, 1622, 1519, 1431, 1383, 1354, 1301 cm^{-1} ; ^1H and ^{13}C NMR data, see Table 3; ESIMS m/z 379 $[\text{M}-\text{H}]^-$; HR-ESIMS m/z 379.2136 $[\text{M}-\text{H}]^-$ (calcd for $\text{C}_{21}\text{H}_{31}\text{O}_6$, 379.2126).

3.3.4 Hyperfaberol D (4)

Yellow gum; $[\alpha]_D^{20}$ –23 (*c* 0.16, MeOH); UV (MeOH) $\lambda_{\max}$ (log ϵ) 291 (3.86), 196 (4.06) nm; IR (KBr) $\nu_{\max}$ 3427, 2969, 2929, 2876, 2730, 1602, 1519, 1384, 1296, 1140, 1034 cm^{-1} ; ^1H and ^{13}C NMR data, see Table 3; ESIMS m/z 347 $[\text{M}-\text{H}]^-$; HR-ESIMS m/z 347.1871 (calcd for $\text{C}_{20}\text{H}_{27}\text{O}_5$, 347.1864).

3.3.5 Hyperfaberol E (5)

Yellow gum; $[\alpha]_D^{20}$ –19 (*c* 0.20, MeOH); UV (MeOH) $\lambda_{\max}$ (log ϵ) 290 (3.23), 228 (3.15), 197 (3.39) nm; IR (KBr) $\nu_{\max}$ 3428, 2966, 2932, 2873, 1623, 1518, 1433, 1354, 1238, 1171, 1023 cm^{-1} ; ^1H and ^{13}C NMR data, see Table 4; ESIMS m/z 347 $[\text{M}-\text{H}]^-$; HR-ESIMS m/z 347.1876 $[\text{M}-\text{H}]^-$ (calcd for $\text{C}_{20}\text{H}_{27}\text{O}_5$, 347.1864).

3.3.6 Hyperfaberol F (6)

Yellow powder; $[\alpha]_D^{20}$ –12 (*c* 0.10, MeOH); UV (MeOH) $\lambda_{\max}$ (log ϵ) 294 (3.82), 250 (4.19), 227 (4.14), 202 (4.31) nm; IR (KBr) $\nu_{\max}$ 3417, 3093, 3071, 2967, 2934, 2878, 2726, 2633, 1622, 1107, 1011 cm^{-1} ; ^1H and ^{13}C NMR data, see Table 5; ESIMS m/z 233 $[\text{M}-\text{H}]^-$; HR-ESIMS m/z 233.0823 $[\text{M}-\text{H}]^-$ (calcd for $\text{C}_{13}\text{H}_{13}\text{O}_4$, 233.0819).

3.3.7 Cytotoxicity Assay

The cytotoxic assay with taxol as a positive control was conducted by MTT method in 96-well plates reported previously (Biological Assay, Supporting Information) [7].

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Compliance with Ethical Standards

Conflict of Interest All authors declare no conflict of interest.

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