JOURNAL OF ASIAN NATURAL PRODUCTS RESEARCH
2022, VOL. 24, NO. 11, 1008–1017
https://doi.org/10.1080/10286020.2021.2016716

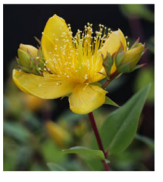
Four new polyprenylated acylphloroglucinol derivatives from *Hypericum beanii*

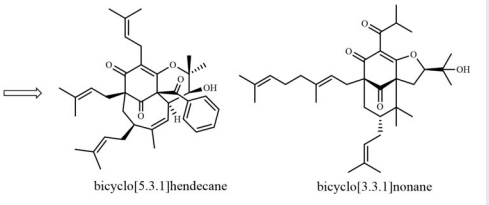
Xin-Yue Suo[a]*, Xiao-Yu Liu[a]*, Xiao-Wei Liu[b], Xiao-Xiu Li[c], Ting-Ting Zhu[a], Teng-Fei Ji[a] and Bo Liu[c]

[a]State Key Laboratory of Bioactive Substance and Function of Natural Medicines, Institute of Materia Medica, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing 100050, China; [b]Beijing Lianxin Pharmaceutical Co., Ltd, Beijing 102600, China; [c]School of Pharmacy, Shenyang Medical College, Shenyang 110034, China

ABSTRACT

Two new polycyclic polyprenylated acylphloroglucinols (PPAPs), hyperbeanins P-Q (**1-2**), and two new biosynthetic precursors, hyperbeanins R-S (**3-4**), were isolated from *Hypericum beanii*, together with three known analogs (**5-7**). Compound **1** was one of type A PPAPs featured with unusual bicyclo[5.3.1]hendecane core. The structures of isolates were established by NMR spectroscopic methods, experimental electronic circular dichroism (ECD) spectra and comparisons with known compounds. Compounds **5** and **6** showed obvious hepatoprotective activity at 10 μM against paracetamol-induced HepG2 cell damage.





ARTICLE HISTORY
Received 19 September 2021
Accepted 5 December 2021

KEYWORDS
Hypericum beanii; PPAPs; ECD; hepatoprotective activity

1. Introduction

Polycyclic polyprenylated acylphloroglucinols (PPAPs), prominent secondary metabolites of the genus *Hypericum*, are a group of structurally fascinating natural products, which feature a phloroglucinol core decorated with prenyl, geranyl, or more substituted side chains [1, 2]. Up to now, more than 900 natural PPAPs with diverse carbon skeletons have been isolated. Apart from their structures, these compounds exhibit a broad range of biological activities, such as anti-tumor, antioxidant,

CONTACT Bo Liu liubopaul@163.com School of Pharmacy, Shenyang Medical College, Shenyang 110034, China; Teng-Fei Ji jitf@imm.ac.cn State Key Laboratory of Bioactive Substance and Function of Natural Medicines, Institute of Materia Medica, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing 100050, China.
*X. S. and X. L. contributed equally.

Supplemental data for this article is available online at https://doi.org/10.1080/10286020.2021.2016716.

antidepressant, antimicrobial, anti-inflammatory, and anti-neurodegenerative effects [3–8], which have attracted extensive attention from the phytochemical, organic synthetic, and pharmacological communities [9–15].

Hypericum beanii, is mainly distributed in Guangxi, Yunnan, and Guizhou provinces in China. As a kind of traditional chinese medicine, it has been used to treat hepatitis, burns, diarrhea, and snake bites [16, 17]. Former studies on the components of *H. beanii* merely resolved some xanthones, triterpenoids, and acylphloroglucinol derivatives [18–21].

2. Results and discussion

In our present study, two new polycyclic polyprenylated acylphloroglucinols (PPAPs), hyperbeanins P-Q (**1**-**2**), and two new biosynthetic precursors of PPAPs, hyperbeanins R-S (**3**-**4**) were isolated from *Hypericum beanii*, together with three known analogs (**5**-**7**). Compound **1** possessed a bicyclo[5.3.1]hendecane core, which was unusual in Type A PPAPs. Additionally, compounds **5** and **6** showed obvious hepatoprotective activity at 10 μM against paracetamol-induced HepG2 cell damage.

Hyperbeanin P (**1**) was obtained as colorless oil. Its molecular formula $C_{38}H_{48}O_5$ was established by HRESIMS (*m/z* 585.3563 $[M+H]^+$), indicating 15 degrees of unsaturation. The IR spectrum showed obvious absorption bands for hydroxyl (3498 cm^{-1}), carbonyl (1715 cm^{-1}), and olefinic groups (1616 cm^{-1}). Its 1 D NMR spectra revealed characteristic resonances of a typical bicyclic PPAP, including an enolized 2,4-diketone moiety [δ_C 166.1 (C-2), 125.0 (C-3), 199.7 (C-4)], a nonconjugated ketone [δ_C 204.7 (C-9)], and three olefinic protons of isoprenyl moieties [δ_H 5.11 (1H, t, $J=7.6$ Hz), 4.90 (1H, t, $J=6.4$ Hz), 4.73 (1H, t, $J=7.6$ Hz)]. Moreover, the ^{1}H NMR signals [δ_H 7.78 (2H, d, $J=7.6$ Hz), 7.44 (1H, t, $J=7.6$ Hz), 7.31 (2H, t, $J=7.6$ Hz)] (Table 1) and the HMBC correlations from H-12/H-16 (δ_H 7.78) to C-10 suggested the presence of an unsubstituted benzoyl moiety (Figure 1).

Table 1. ^{1}H NMR and ^{13}C NMR spectral data for compounds **1**–**2**.[a]

	1		2			1		2	
No	δ_C	δ_H (*J* in Hz)	δ_C	δ_H (*J* in Hz)	No	δ_C	δ_H (*J* in Hz)	δ_C	δ_H (*J* in Hz)
1	74.6		71.8		20	26.1	1.73 s	119.5	5.08 t (7.2)
2	166.1		173.3		21	18.1	1.66 s	138.2	
3	125.0		120.3		22	40.0	2.70 dd (13.2, 8.4); 2.37 dd (13.2, 8.4)	40.2	1.91-2.02 m
4	199.7		191.3		23	118.2	4.73 t (7.6)	16.5	1.67 s
5	62.8		62.5		24	136.1		26.9	1.99-2.02 m
6a	43.4	2.37 d (7.2);	38.9	2.13 dd (14.4, 7.2);	25	26.2	1.54 s	124.5	5.05 t (7.2)
6b		1.43 t (12.8)		1.91-2.02 m					
7	39.0	2.56-2.63 m	48.3	1.41-1.43 m	26	17.7	1.38 s	131.4	
8	145.8		47.1		27	32.9	1.95-2.14 m	17.8	1.57 s
9	204.7		206.7		28	122.0	4.90 t (6.4)	26.0	1.64 s
10	195.5		27.4	3.01 dd (14.8, 10.4); 2.87 dd (14.8, 10.4)	29	133.6		29.6	2.17-2.25 m; 1.91-2.02 m
11	136.8		94.1	4.80 t (10.4)	30	25.9	1.70 s	124.7	4.89 t (7.6)
12	128.4	7.78 d (7.6)	71.3		31	18.3	1.59 s	132.9	
13	128.6	7.31 t (7.6)	23.4	1.38 s	32	19.3	1.65 s	25.9	1.66 s
14	132.8	7.44 t (7.6)	25.4	1.25 s	33	134.6	5.94 d (9.6)	18.0	1.55 s
15	128.6	7.31 t (7.6)	208.7		34	51.5	3.66 t (10.4)	23.4	1.36 s
16	128.4	7.78 d (7.6)	40.0	2.50 sept (6.8)	35	73.2	4.42 d (10.8)	26.9	1.28 s
17	22.6	3.19-3.25 m	21.1	1.15 d (6.8)	36	90.8			
18	120.7	5.11 t (7.6)	21.1	1.11 d (6.8)	37	28.5	1.34 s		
19	133.2		29.5	2.46 d (7.2)	38	19.9	1.31 s		

[a]Recorde in $CDCl_3$ (^{1}H NMR 400 MHz, ^{13}C NMR 125 MHz).

Comprehensive interpretation of its 2 D NMR data disclosed the planar structure of **1**. The bicyclo[5.3.1]hendecane core of **1** was resolved by HMBC correlations (Figure 2) from H-6 (δ_H 1.43/2.37) to C-4/C-5/C-7/C-8/C-9, from H-7 (δ_H 2.60) to C-5/C-6/C-8/C-32/C-33, from H-32 (δ_H 1.65) to C-7/C-8/C-33, from H-33 (δ_H 5.94) to C-7/C-32/C-34, and from H-34 (δ_H 3.66) to C-1/C-2/C-8/C-33, together with the ^{1}H-^{1}H COSY cross-peaks of H-6/H-7 and H-33/H-34. In addition, The HMBC correlations (Figure 2) from H-35 (δ_H 4.42) to C-1/C-33/C-34/C-36, from Me-37/Me-38 to C-35/C-36, and from Me-37 (δ_H 1.34) to C-2 defined the remaining *gem*-dimethyl tetrahydropyran moiety in **1**. The locations of three isoprenyl groups at C-3, C-5, and C-7 were assigned by HMBC spectrum as well. These observations suggested that compound **1** and hypercohin A shared the same planar structure [22].

The C-7 chemical shift (δ_C 39.0) and the chemical shift difference between H-6a and H-6b ($\Delta\delta$ ca. 0.94) were in accordance with the classical reported rules [2], and it implied that the C-7 substituent was exo. Moreover, the ROESY correlations (Figure 3) of H-7 (δ_H 2.60)/H-34 (δ_H 3.66), and H-34 (δ_H 3.66)/H-35 (δ_H 4.42) indicated that H-7, H-34, and H-35 were α-oriented as shown in Figure 1, suggesting

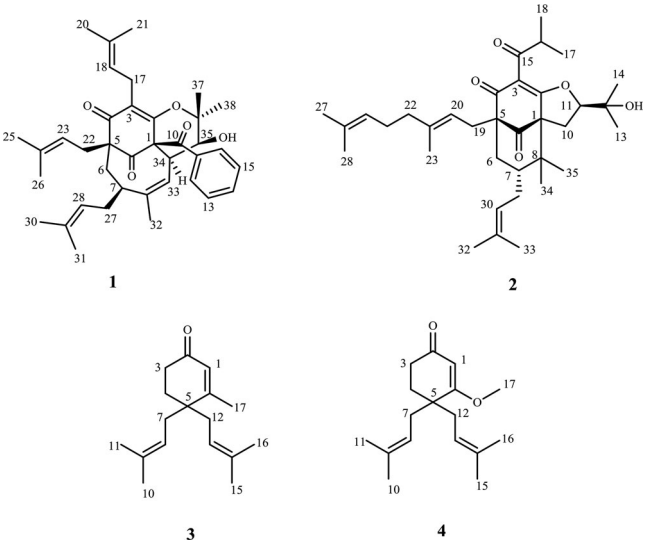


Figure 1. Structures of compounds **1**–**4**.

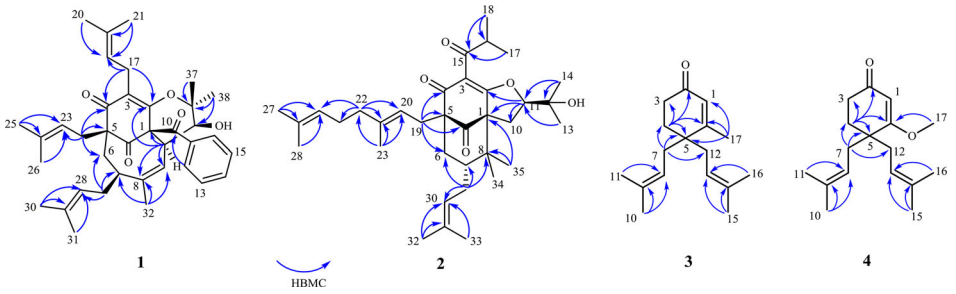


Figure 2. Key HMBC correlations for **1**–**4**.

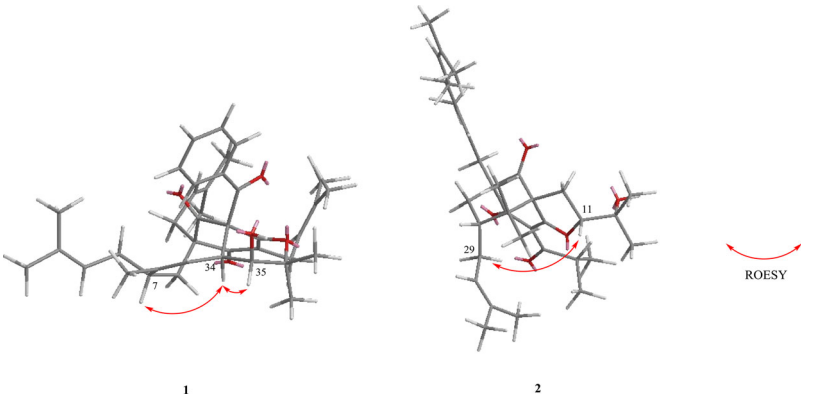


Figure 3. Key ROESY correlations for **1–2**.

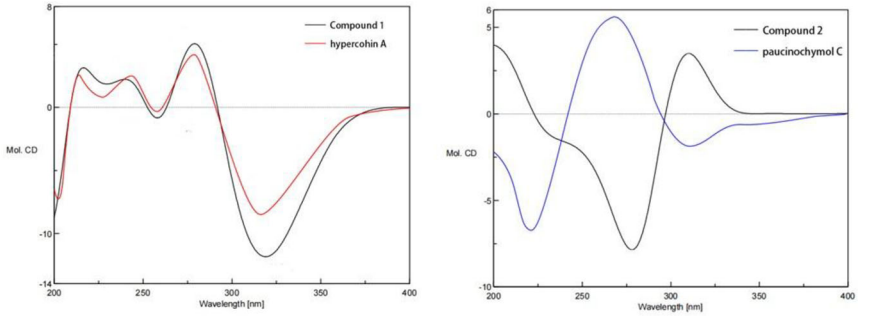


Figure 4. The experimental ECD spectra of **1** and **2**.

that **1** was the C-35 epimer of hypercohin A. The absolute configurations of **1** were elucidated by comparison of ECD spectrum with that of hypercohin A (Figure 4), whose absolute configurations had been unambiguously determined by X-ray diffration analysis [22]. Therefore, the absolute configurations of **1** was defined as 1*S*, 5*R*, 7*S*, 34*S*, and 35*S*.

The molecular formula of hyperbeanin Q (**2**) was established as $C_{35}H_{52}O_5$ according to its HRESIMS data (*m/z* 553.3884 $[M+H]^+$), indicating 10 degrees of unsaturation. The ^{1}H NMR spectrum (Table 1) displayed signals for three olefinic protons [δ_H 5.08 (1H, t, $J=7.2$ Hz), 5.05 (1H, t, $J=7.2$ Hz), 4.89 (1H, t, $J=7.6$ Hz)], an isopropyl group [δ_H 2.50 (1H, sept, $J=6.8$ Hz), 1.15 (1H, d, $J=6.8$ Hz), 1.11 (1H, d, $J=6.8$ Hz)], and nine methyl groups [δ_H 1.67, 1.66, 1.64, 1.56, 1.55, 1.38, 1.36, 1.28, 1.25]. The characteristic ^{13}C NMR resonances of enolized 2,4,15-triketone moiety [δ_C 173.3 (C-2), 120.3 (C-3), 191.3 (C-4), 208.7 (C-15)], suggested a type B PPAP skeleton of **2**. The HMBC correlations from H-11 (δ_H 4.80) to C-1/C-2/C-10 indicated that a dihydrofuran ring was formed between C-1 and C-2. The geranyl and isoprenyl groups were located at C-5 and C-7 respectively, suggested by the HMBC correlations from H_2-19 (δ_H 2.46) to C-4/C-5/C-6/C-9, and from H_2-29 (δ_H 2.21/1.95) to C-6/C-7/C-8. These observations revealed the structure of **2** closely resembled that of paucinochymol C, differing in the isopropyl group at C-3 instead of 3,4-dihydroxybenzoyl

group [23]. On the basis of C-7 chemical shift (δ_C 48.3) and the small difference in chemical shifts of the two H-6 atoms ($\Delta\delta$ ca. 0.20) [2], as well as the ROESY correlation (Figure 3) of H-11 (δ_H 4.80)/H_2-29 (δ_H 2.21/1.95), the relative configurations of **2** were established to be the same as paucinochymol C. Contrary to paucinochymol C, the ECD spectrum of **2** exhibited negative excition chirality at round 240-280 nm (Figure 4). This observation indicated that the absolute configurations of C-1 and C-5 in **2** were 1*S* and 5*S*, respectively. Thus, the absolute configurations of **2** were defined as 1*S*, 5*S*, 7 *R*, and 11 *R*.

Hyperbeanin R (**3**) was obtained as colorless oil. Its molecular formula $C_{17}H_{26}O$ was established by the HRESIMS (*m/z* 247.2060 $[M+H]^+$), indicating 5 degrees of unsaturation. The ^{1}H NMR spectrum (Table 1) exhibited three olefinic protons [δ_H 5.89 (1H, s), 5.06 (2H, t, $J = 4.8$ Hz)] and five methyl groups [δ_H 1.92, 1.71 × 2, 1.62 × 2]. The ^{13}C NMR spectrum displayed 17 carbon signals, including a carbonyl carbon [δ_C 199.8 (C-2)] and six olefinic carbons [δ_C 128.9 (C-1), 168.0 (C-6), 119.8 (C-8 and C-13), 134.7 (C-9 and C-14)]. The structure of **3** was deduced due to the key HMBC correlations from H_3-10 (δ_H 1.62)/H_3-11 (δ_H 1.71) to C-8/C-9, from H_2-7 (δ_H 2.22) to C-4/C-5/C-6/C-8/C-9, from H_3-17 (δ_H 1.92) to C-1/C-5/C-6, from H-1 (δ_H 5.89) to C-2/C-3/C-5/C-6, and from H_2-4 (δ_H 1.85) to C-2/C-3/C-5/C-6/C-7 as shown in Figure 2.

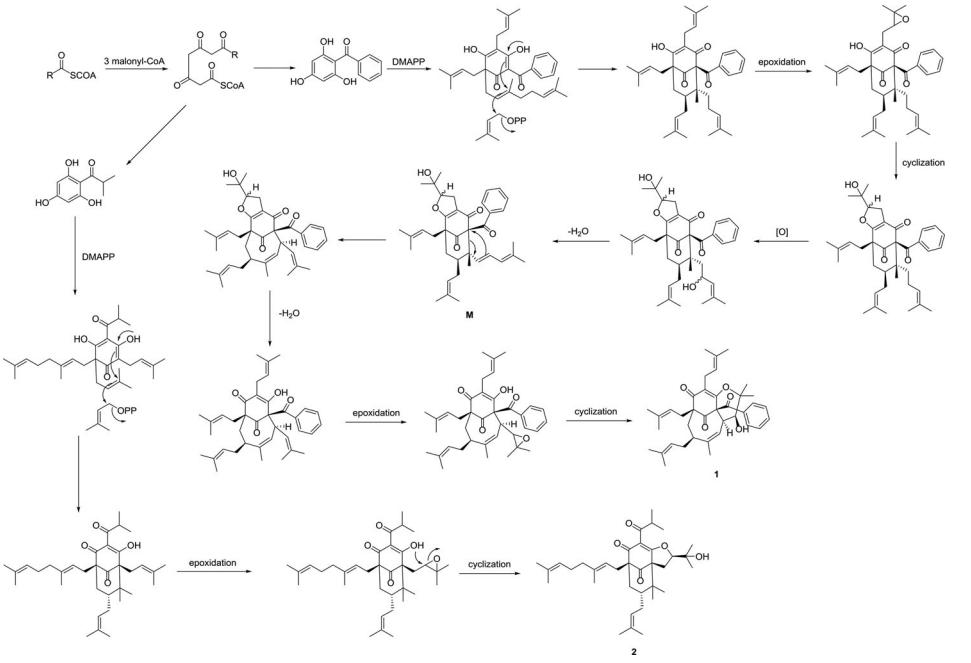
Hyperbeanin S (**4**) was obtained as colorless oil. Its molecular formula $C_{17}H_{26}O_2$ was established by the HRESIMS (*m/z* 263.2010 $[M+H]^+$), indicating 5 degrees of unsaturation. By analysis of 1 D and 2 D NMR data (Table 2), compound **4** was shown to possess the same backbone as **3**. The difference of **4** was the presence of a methoxyl group at C-3 rather than a methyl group in **3**.

Additionally, another three isolates were identified to be known compounds such as uralodin A (**5**) [24], 13,14-didehydroxyguttiferone A (**6**) [19], and 3-methyl-4-(3-methyl-2-buten-1-yl)-2-cyclohexen-1-one (**7**) [25] by comparing their spectroscopic data with those reported in the literature.

Table 2. ^{1}H NMR and ^{13}C NMR spectral data for compounds **3**-**4**[a].

No	3 δ_C	δ_H (*J* in Hz)	4 δ_C	δ_H (*J* in Hz)
1	128.9	5.89 s	101.8	5.29 s
2	199.8		203.5	
3	34.4	2.40 t (5.6)	25.9	2.40 t (6.0)
4	30.6	1.85 t (5.6)	28.9	1.83 t (6.4)
5	43.2		48.0	
6	168.0		176.7	
7	36.0	2.22 d (5.6)	33.8	2.27 dd (14.4, 7.2); 2.15 dd (14.4, 7.2)
8	119.8	5.06 t (4.8)	120.0	5.07 t (7.2)
9	134.7		134.1	
10	26.2	1.62 s	26.2	1.58 s
11	18.2	1.71 s	18.1	1.68 s
12	36.0	2.22 d (5.6)	33.8	2.27 dd (14.4, 7.2); 2.15 dd (14.4, 7.2)
13	119.8	5.06 t (4.8)	120.0	5.07 t (7.2)
14	134.7		134.1	
15	26.2	1.62 s	26.2	1.58 s
16	18.2	1.71 s	18.1	1.68 s
17	20.6	1.92 s	55.7	3.67 s

[a]Recorde in $CDCl_3$ (^{1}H NMR 400 MHz, ^{13}C NMR 125 MHz).



Scheme 1. Plausible biosynthetic pathways of **1**–**2**.

The plausible biogenetic pathway for compounds **1-2** is proposed as shown in Scheme 1. Compond **1** was considered to be generated from the representative [3.3.1]-type PPAPs via C[1,3]σ migration rearrangement, followed by dehydration, keto-enol tautomeration, and intramolecular cyclization successively [22]. Similarly, compound **2** could be formed from [3.3.1]-type PPAPs through epoxidation and cyclization.

Compounds **1-7** were evaluated for their hepatoprotective activities against paracetamol-induced HepG2 cell damage, and bicyclol was used as the positive control. As shown in Table 2, compounds **5** and **6** exhibited obvious hepatoprotective activities at 10 μM.

3. Experimental

3.1. General experiment procedures

Optical rotations were measured on a JASCO P-2000 polarimeter (JASCO Inc. Tokyo, Japan). UV spectra were measured on a JASCO V650 spectrophotometer (JASCO Inc.). The ECD spectra were measured on a JASCO J-815 CD spectrometer (JASCO Inc.). IR spectra were recorded on a Nicolet 5700 FT-IR spectrometer (Thermo Nicolet, Waltham, MA, USA). The NMR spectra were acquired with VNS-400 spectrometers and VNS-500 spectrometers (Varian Inc. Palo Alto, CA, USA). HRESI–MS were collected on an Agilent 1100 series LC/MSD ion trap mass spectrometer (Agilent Technologies Ltd, Santa Clara, CA, USA). Preparative HPLC was performed on a Shimadzu LC-6AD instrument with a SPD-20A detector, using an

YMC-Pack ODS-A column (250 × 20 mm, 5 μm; YMC, Tokyo, Japan). Column chromatography was performed with silica gel (200 − 300 mesh, Qingdao Marine Chemical Inc., Qingdao, China) and ODS (50 μm, YMC, Japan). TLC was carried out on plates precoated silica gel GF_{254} (Qingdao Marine Chemical Inc.). Spots were visualized under UV light or by sprayingwith 10% sulfuric acid in EtOH followed by heating.

3.2. Plant material

The air-dried aerial parts of *Hypericum beanii* were purchased from Kunming, Yunnan Province, China, in August 2017. Prof. Lin Ma was responsible for the identification of the plant. A voucher specimen (No. ID-24237) was deposited in the Institute of Materia Medica, Chinese Academy of Medical Sciences.

3.3. Extraction and isolation

The air-dried aerial parts of *H. beanni* (30 kg) were extracted by 95% ethanol (150 L × 3 times) under reflux. The crude extract was suspended in H_2O and partitioned with petroleum ether (PE). The PE extract (998.7 g) was separated on a silica gel column (PE/EtOAc, 100:0 to 0:100) to gain 9 fractions (Fr.1-9). Fr.1 (250.0 g) was further purified by chromatography on a diol column, eluting with PE/EtOAc (100:0 to 0:100) to yield 13 fractions (Fr.1.1-Fr.1.13). Fr.1.5 (14.0 g) was fractionated using a Sephadex LH-20 column with PE/CH_2Cl_2/MeOH (5:5:1) as eluent to give 6 fractions (Fr.1.5.1-Fr.1.5.6), Fr.1.5.4 was purified by preparative TLC with PE/CH_2Cl_2 (2:1) to yield **6** (10.0 mg). Fr.1.9 (16.7 g) was fractionated using an ODS column with MeOH/H_2O (80:20 to 100:0) as eluent to give 4 fractions (Fr.1.9.1-Fr.1.9.4), Fr.1.9.4 (9.9 g) was purified by semi-preparative HPLC (MeCN/H_2O, 84:16 to 86:14) to yield **3** (23 mg, t_R = 35.3 min), **4** (4 mg, t_R = 38.1 min), and **7** (16 mg, t_R = 36.8 min). Fr.3 (150.3 g) was purified over MCI column (EtOH/H_2O, 80:20 to 95:5) to yield 9 fractions (Fr.3.1-Fr.3.9). Fr.3.4 (7.2 g) was fractionated using an ODS column with MeOH/H_2O (70:30 to 100:0) as eluent to give 6 fractions (Fr.3.4.1-Fr.3.4.6). Then Fr.3.4.4 (1.5 g) was purified by semi-preparative HPLC (MeOH/H_2O, 92:8 to 96:4) to yield **1** (23 mg, t_R = 30.2 min), **2** (16 mg, t_R = 32.7 min), **5** (10 mg, t_R = 36.4 min).

3.3.1. Hyperbeanin P (1)

Colorless oil; $[\alpha]_D^{25}$ −254 (*c* 0.2, MeOH); UV (MeOH) λ_{max} (log ε) 204 (4.52), 248 (4.27) nm; ECD (MeOH) $\Delta\varepsilon_{216\,nm}$ + 3.13, $\Delta\varepsilon_{240\,nm}$ + 2.22, $\Delta\varepsilon_{258\,nm}$ − 0.85, $\Delta\varepsilon_{279\,nm}$ + 5.04, $\Delta\varepsilon_{319\,nm}$ − 11.86; IR (KBr) ν_{max} 3498, 2969, 2920, 1715, 1616, 1445, 1376 cm^{-1}; ^1H and ^{13}C NMR spectral data, see Table 1; HRESIMS: *m/z* 585.3563 $[M+H]^+$ (calcd for $C_{38}H_{49}O_5$, 585.3575).

3.3.2. Hyperbeanin Q (2)

Colorless oil; $[\alpha]_D^{25}$ −19.5 (*c* 0.4, MeOH); UV (MeOH) λ_{max} (log ε) 204 (3.93), 283 (3.55) nm; ECD (MeOH) $\Delta\varepsilon_{278\,nm}$ − 7.86, $\Delta\varepsilon_{310\,nm}$ + 3.74; IR (KBr) ν_{max} 3347,

Table 3. Hepatoprotective effects of compounds **1**–**7** (10 μM) against paracetamol-induced HepG2 cell damage.[a]

compound	cell viability (% normal)	Inhibition rate (% of control)
normal	100.0	
control	54.9	
bicyclol	66.1	20.2
1	47.2	−14.0
2	53.4	−2.7
3	57.8	5.3
4	55.1	0.3
5	61.3[b]	11.7
6	65.8[c]	19.9
7	55.1	0.3

[a]Results are expressed as the means ± SD (n = 3, for normal and control, n = 6); bicyclol was used as positive control (10 μM). [b]$p < 0.05$. [c]$p < 0.01$.

2925, 1615, 1447, 1379 cm^{-1}; ^1H and ^{13}C NMR spectral data, see Table 1; HRESIMS: *m/z* 553.3884 $[M+H]^+$ (calcd for $C_{35}H_{53}O_5$, 553.3888).

3.3.3. Hyperbeanin R (3)

Colorless oil; UV (MeOH) λ_{max} (log ε) 202 (3.91), 251 (4.09) nm; IR (KBr) ν_{max} 2926, 1653, 1614, 1380, 1196 cm^{-1}; ^1H and ^{13}C NMR spectral data, see Table 1; HRESIMS: *m/z* 247.2060 $[M+H]^+$ (calcd for $C_{17}H_{27}O$, 247.2056).

3.3.4. Hyperbeanin S (4)

Colorless oil; UV (MeOH) λ_{max} (log ε) 202 (4.01), 251 (4.17) nm; IR (KBr) ν_{max} 3416, 2926, 1724, 1622, 1447, 1223 cm^{-1}; ^1H and ^{13}C NMR spectral data, see Table 1; HRESIMS: *m/z* 263.2010 $[M+H]^+$ (calcd for $C_{17}H_{27}O_2$, 263.2006).

3.4. Hepatoprotection bioassays (in vitro)

The hepatoprotective effects of compounds **1-7** were determined by a (MTT) colorimetric assay in HepG2 cells. Each cell suspension of 2×10^4 cells in 200 μl of RPMI 1640 containing fetal calf serum (10%), penicillin (100 U/ml), and streptomycin (100 μg/ml) was placed in a 96-well microplate and pre-cultured for 24 h at 37 °C under 5% CO_2 atmosphere. Fresh medium (100 μl) containing bicyclol and test samples was added respectively, and the cells were cultured for 1 h. The cultured cells were exposed to 8 mM paracetamol for 24 h. Then, 100 μl of 0.5 mg/ml MTT was added to each well after the withdrawal of the culture medium and incubated for additional 4 h. The resulting formazan was dissolved in 150 μl DMSO after aspiration of the culture medium. The optical density (OD) of the formazan solution was measured on a microplate reader at 570 nm. Percent inhibition was calculated as: Inhibition (%) = [OD (sample) - OD (control)]/[OD (normal) - OD (control)] × 100% (Table 3).

Disclosure statement

No potential conflict of interest was reported by the authors.

Funding

The project was financially supported by Projects of International Cooperation and Exchanges NSFC (NSFC-VR, No. 81361138020), National Science and Technology Major Projects for "Major New Drugs Innovation and Development", Research and Development of New Drug Varieties from Natural Product Sources and Their Key Innovative Technological Systems (No. 2018ZX09711001-001-001 and 2018ZX09711001-001-003) and the CAMS Innovation Fund for Medical Sciences (CIFMS), the CAMS Initiative for Innovative Medicine (CAMS-I2M, No. 2016-I2M-1-010). Shenyang young and middle-aged talent project (RC210485).

ORCID

Bo Liu http://orcid.org/0000-0003-4755-3828

References

[1] I.P. Singh, and S.B. Bharate, *Nat. Prod. Rep.* **23**, 558 (2006).
[2] R. Ciochina, and R.B. Grossman, *Chem. Rev.* **106**, 3963 (2006).
[3] D.S. Tian, P. Yi, L. Xia, X. Xiao, Y.M. Fan, W. Gu, L.J. Huang, Y.B. David, Y.T. Di, C.M. Yuan, and X.J. Hao, *Org. Lett.* **18**, 5904 (2016).
[4] L. Verotta, *Phytochem. Rev.* **1**, 389 (2002).
[5] Z. Saddiqe, I. Naeem, and A. Maimoona, *J. Ethnopharmacol.* **131**, 511 (2010).
[6] G.M. Raso, M. Pacilio, G.D. Carlo, E. Esposito, L. Pinto, and R. Meli, *J. Pharm. Pharmacol.* **54**, 1379 (2010).
[7] Y. Guo, N. Zhang, C.M. Chen, J.F. Huang, X.N. Li, J.J. Liu, H.C. Zhu, Q.Y. Tong, J.W. Zhang, Z.W. Luo, Y.B. Xue, and Y.H. Zhang, *J. Nat. Prod.* **80**, 1493 (2017).
[8] J.A. Richard, R.H. Pouwer, and D.Y. Chen, *Angew. Chem. Int. Ed. Engl.* **51**, 4536 (2012).
[9] H.P. Pepper, S.J. Tulip, Y. Nakano, and J.H. George, *J. Org. Chem.* **79**, 2564 (2014).
[10] X.W. Yang, R.B. Grossman, and G. Xu, *Chem. Rev.* **118**, 3508 (2018).
[11] J.B. Yang, R.D. Liu, J. Ren, Q. Wei, A.G. Wang, and Y.L. Su, *J. Asian Nat. Prod. Res.* **18**, 436 (2016).
[12] R.D. Liu, J. Ma, J.B. Yang, A.G. Wang, and Y.L. Su, *J. Asian Nat. Prod. Res.* **16**, 717 (2014).
[13] W. Gao, J.W. Hu, W.Z. Hou, F. Xu, J. Zhao, F. Xu, H. Sun, J.G. Xing, Y. Peng, X.L. Wang, T.F. Ji, L. Li, and Z.Y. Gu, *Tetrahedron Lett.* **57**, 2244 (2016).
[14] H.R. Sun, J.J. Wang, B. Zhen, X. Wang, X.Y. Suo, M.B. Lin, J.D. Jiang, and T.F. Ji, *J. Asian Nat. Prod. Res.* **23**, 536 (2021).
[15] X.Y. Suo, M.J. Shi, J. Dang, H.L. Yue, Y.D. Tao, B. Zhen, J.J. Wang, X. Wang, H.R. Sun, H. Sun, G.F. Qiang, T.F. Ji, and B. Liu, *J. Asian Nat. Prod. Res.* **23**, 1068 (2021).
[16] Editorial committee of the Administration Bureau of Traditional Chinese Medicine. *Chinese Materia Medica (Zhonghua Bencao)* (Shanghai Science and Technology Press, Shanghai, 1999), Vol. 596.
[17] J.F. Zeng, and C.Y. Huo, *Flora Reipublicae Popularis Sinicae (Zhongguo Zhiwu Zhi)* (Science Press, Beijing, 2004), pp. 36–38.
[18] J.J. Zhang, X.W. Yang, J.Z. Ma, Y. Ye, X.L. Shen, and G. Xu, *Tetrahedron* **71**, 8315 (2015).
[19] W.J. Xu, P.F. Tang, W.J. Lu, Y.Q. Zhang, X.B. Wang, H. Zhang, J. Luo, and L.Y. Kong, *Org. Lett.* **21**, 8558 (2019).
[20] Y.R. Li, W.J. Xu, S.S. Wei, W.J. Lu, J. Luo, and L.Y. Kong, *Phytochemistry* **159**, 56 (2019).

[21] B. Zhen, X. Suo, J. Dang, H. Yue, Y. Tao, J.J. Wang, L. Li, M.B. Lin, Q. Hou, W.P. Wang, X.L. Wang, J.D. Jiang, and T.F. Ji, *Chin. Chem. Lett.* **32**, 2338 (2021).
[22] X.W. Yang, X. Deng, X. Liu, C.Y. Wu, X.N. Li, B. Wu, H.R. Luo, Y. Li, H.X. Xu, Q.S. Zhao, and G. Xu, *Chem. Commun. (Camb)* **48**, 5998 (2012).
[23] X. Tan, F. Zhong, H. Teng, Q. Li, Y. Li, Z. Mei, Y. Chen, and G. Yang, *Fitoterapia* **146**, 104688 (2020).
[24] N. Guo, X.Q. Chen, and Q.S. Zhao, *Acta Bot. Yunnan* **4**, 515 (2008).
[25] S.J. Spessard, and B.M. Stoltz, *Org. Lett.* **4**, 1943 (2002).