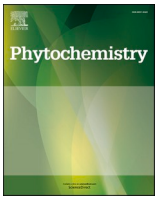
Phytochemistry 203 (2022) 113413

Contents lists available at ScienceDirect

Phytochemistry

journal homepage: www.elsevier.com/locate/phytochem



Polycyclic polyprenylated acylphloroglucinols from *Hypericum beanii* and their hepatoprotective activity

Yonghui Ma [a,b,1], Xinyue Suo [a,1], Xiaoxiu Li [c], Tingting Zhu [a], Jin Li [b,***], Tengfei Ji [a,d,**], 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, People's Republic of China
[b] The Key Laboratory of Plant Stress Biology in Arid Land, College of Life Sciences, Xinjiang Normal University, Ürümqi, Xinjiang, 830054, People's Republic of China
[c] School of Pharmacy, Shenyang Medical College, Shenyang, Liaoning, 110034, People's Republic of China
[d] Key Laboratory of Tibetan Medicine Research, Northwest Institute of Plateau Biology, Chinese Academy of Sciences, Xining, Qinghai, 810008, People's Republic of China

ARTICLE INFO

Keywords:
Hypericum beanii
Hypericaceae
PPAPs
Hyperbeanin A-G
Hepatoprotective activity

ABSTRACT

Twenty-seven polycyclic polyprenylated acylphloroglucinols (PPAPs) with diverse skeletons, including seven previously undescribed ones (hyperbeanins A-G), were isolated from the aerial parts of *Hypericum beanii*. Their structures were established by comprehensive analysis of NMR, HRESIMS, and experimental electronic circular dichroism (ECD) spectra. Hyperbeanin A was a monocyclic polyprenylated acylphloroglucinols (MPAPs) with an unusual spiro-fused cyclopropane ring. Four of the isolated compounds showed obvious hepatoprotective activity against paracetamol-induced HepG2 cell damage at 10 μM. The present results suggested that these compounds would be potential hepatoprotective agents. In addition, the plausible biogenetic pathways of hyperbeanins A-G were proposed, which gave an insight for future biomimetic synthesis of them.

1. Introduction

As a genus of the Hypericaceae family, *Hypericum* is well-known for its extensive medicinal and horticultural exploitation. Almost 500 species of *Hypericum* distributed all over the world (Nürk et al., 2013), many of which are used in folk medicine as remedies for wound healing, burns, and gastrointestinal tract inflammation (Silva et al., 2005). The best-known and extensively studied member of this genus is *H. perforatum* L. (St John's wort), which is applied for treating mild and moderate depression (Whiskey et al., 2001). Polycyclic polyprenylated acylphloroglucinols (PPAPs), as the main specialised metabolites of *Hypericum*, possess highly oxygenated acylphloroglucinol-derived cores decorated with prenyl or geranyl side chains. Moreover, these metabolites exhibit a broad range of biological activities, such as antidepressant, anti-inflammatory, anticancer, antioxidant, antibacterial, antiulcer, antimalarial, and antineurodegenerative (Raso et al., 2002; Verotta, 2002; Saddiqe et al., 2010; Richard et al., 2012; Tian et al., 2016; Guo et al., 2017).

Hypericum beanii N. Robson is a perennial herbaceous shrub of this genus and mainly cultivated in Guizhou and Yunnan Provinces of China. In addition to its ornamental value, *H. beanii* is used for the treatment of hepatitis, burns, diarrhea, and snake bites as a traditional medicine (Editorial Committee of the Administration Bureau of Traditional Chinese Medicine, 1999). Previous chemical investigation on this plant revealed that a series of complex phloroglucinols have been isolated, which showed diverse pharmacological activities (Shiu and Gibbons, 2006; Chen et al., 2011; Xu et al., 2019; Li et al., 2019, 2021; Suo et al., 2021). In present study, seven new PPAPs (hyperbeanins A-G, 1–7) with twenty known ones (8–27) were obtained from this plant (Fig. 1). The isolates were classified into four categories: monocyclic polyprenylated acylphloroglucinols (MPAPs) (1–2, 8–10), spirocyclic PPAPs (3, 11), bicyclic polyprenylated acylphloroglucinols (BPAPs) (4–5, 12–20), and

* Corresponding author.
** Corresponding author. 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, People's Republic of China.
*** Corresponding author.
E-mail addresses: xjcjlj4@xjnu.edu.cn (J. Li), jitf@imm.ac.cn (T. Ji), liubopaul@163.com (B. Liu).
[1] These authors contributed equally to this work.

https://doi.org/10.1016/j.phytochem.2022.113413
Received 27 May 2022; Received in revised form 20 August 2022; Accepted 21 August 2022
Available online 28 August 2022
0031-9422/

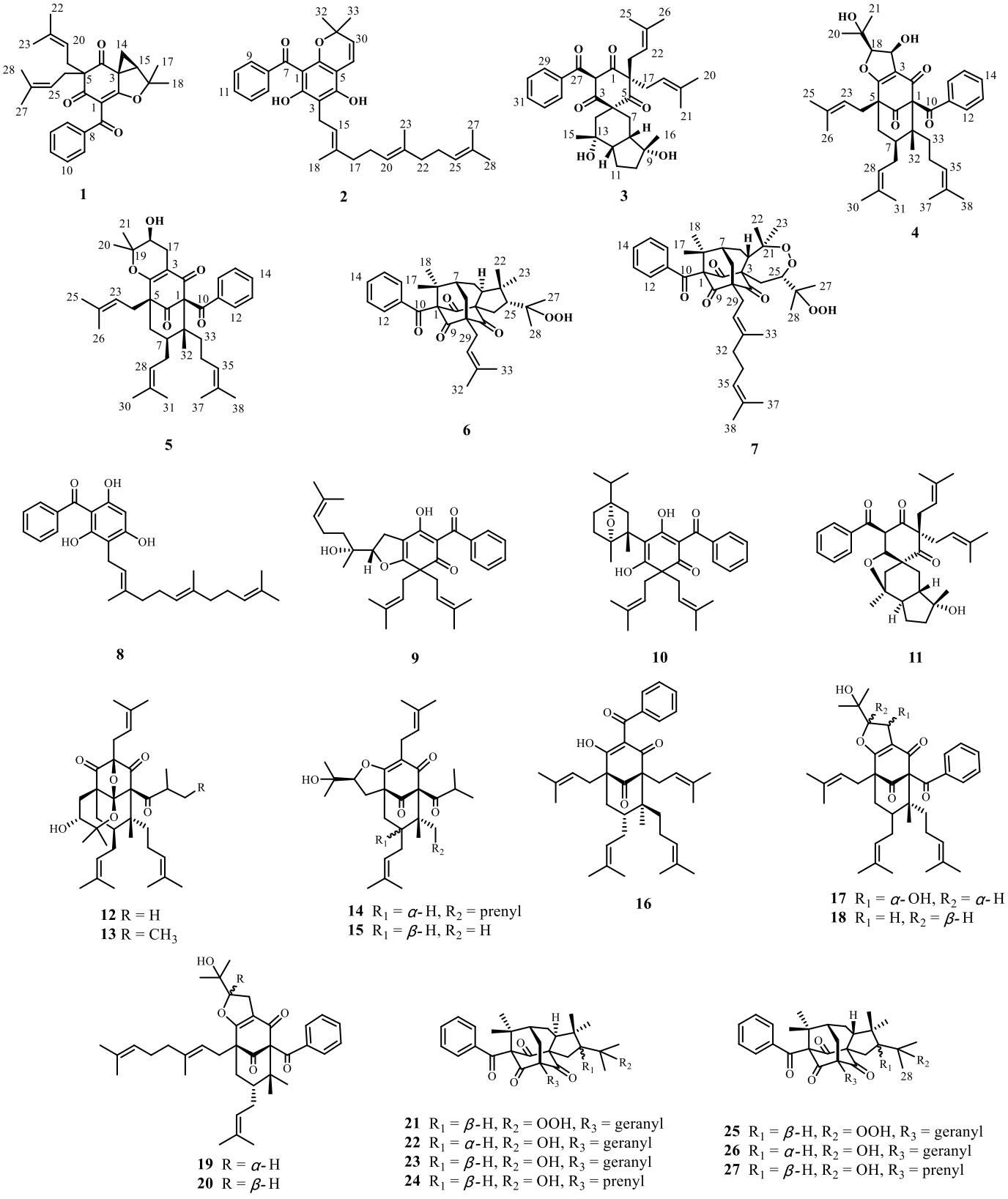


Fig. 1. Chemical structures of 1–27.

homoadamantane-type PPAPs (6–7, 21–27). It is notable that compound 1 possesses an unusual spiro-fused cyclopropane ring. In addition, compounds 8, 16–18 showed obvious hepatoprotective activity against paracetamol-induced HepG2 cell damage at 10 μM. The processes of isolation, purification, elucidation of structures, and bioactivity of these compounds are reported herein.

Table 1
^{1}H NMR and ^{13}C NMR data for compounds 1, 3, 6[a], and 2[b].

No	1		2		3		6	
	δ_H	δ_C	δ_H	δ_C	δ_H	δ_C	δ_H	δ_C
1		117.2		105.4		199.8		80.9
2		173.2		162.2	6.16 s	96.0		203.9
3		41.8		105.2		174.8		73.4
4		207.1		158.3		62.1		206.6
5		65.3		102.0		204.2		69.1
6		196.9		154.7		66.7	1.89 d (14.4); 2.52 m	42.5
7		192.1		200.7	1.65 m; 2.31 m	30.9	2.13 m	43.9
8		137.6		143.0	1.25 m	49.9		51.0
9	7.80 d (5.6)	129.4	7.47 d (7.5)	127.2		77.4		204.9
10	7.41 t (5.6)	128.4	7.38 t (7.5)	127.7	1.70 m; 1.83 m	40.0		192.7
11	7.53 t (5.6)	133.3	7.44 t (7.5)	130.1	1.27 m; 1.68 m	22.4		135.0
12	7.41 t (5.6)	128.4	7.38 t (7.5)	127.7	1.93 m	48.6	7.10 d (7.6)	129.1
13	7.80 d (5.6)	129.4	7.47 d (7.5)	127.2		83.5	7.28 t (7.6)	128.2
14	1.69 m; 1.56 m	27.6	3.45 d (7.0)	21.8	1.95 m; 2.63 m	48.1	7.40 t (7.6)	132.3
15	2.91 dd (6.0, 4.4)	38.1	5.33 t (7.0)	121.8	1.39 s	22.2	7.28 t (7.6)	128.2
16		91.4		140.6	1.30 s	26.9	7.10 d (7.6)	129.1
17	1.37 s	28.2	2.13 m	39.8	2.65 m; 2.88 m	30.6	1.46 s	25.3
18	1.40 s	23.4	1.85 s	16.3	4.87 m	117.7	1.40 s	23.0
19	2.65 m	36.8	2.00 m; 2.06 m	26.8		135.7	2.06 dd (10.8, 8.8)	57.9
20	5.00 t (6.4)	119.0	5.08 m	123.4	1.67 s	26.2	1.64 m; 2.28 m	28.8
21		135.7		136.0	1.58 s	18.2		44.7
22	1.71 s	26.2	1.98 m; 2.05 m	39.9	2.63 m	30.8	0.93 s	28.2
23	1.55 s	18.0	1.61 s	16.4	4.89 m	117.8	1.17 s	27.7
24	2.49 m; 2.68 m	38.8	2.12 m; 2.16 m	26.3		135.7	2.16 dd (12.8, 7.6); 2.49 t (12.4)	33.3
25	5.05 t (6.4)	118.4	5.09 m	124.5	1.66 m	26.2	2.86 dd (12.4, 8.0)	54.5
26		135.6		131.5	1.55 m	18.2		85.9
27	1.68 s	26.2	1.67 s	25.9		179.7	1.36 s	24.8
28	1.55 s	18.0	1.59 s	17.9		133.7	1.40 s	23.1
29			6.47 d (10.0)	116.1	7.86 d (7.0)	127.2	2.55 d (6.8)	29.6
30			5.27 d (10.0)	125.2	7.45 t (7.0)	128.7	5.08 t (7.2)	119.2
31				77.5	7.52 t (7.0)	132.7		135.0
32			0.97 s	27.5	7.45 t (7.0)	128.7	1.68 s	26.3
33			0.97 s	27.5	7.86 d (7.0)	127.2	1.65 s	18.2
2-OH			12.83s					
4-OH			6.40 s					

[a] Recorded in $CDCl_3$ (^{1}H NMR 400 MHz,^{13}C NMR 125 MHz).
[b] Recorded in $CDCl_3$ (^{1}H NMR 500 MHz,^{13}C NMR 125 MHz).

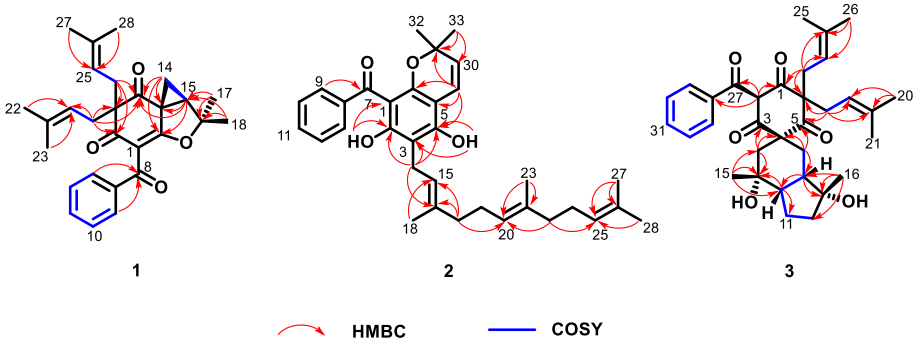


Fig. 2. Key HMBC and ^{1}H–^{1}H COSY correlations of 1–3.

2. Results and discussion

Hyperbeanin A (1) was obtained as colorless oil, and its molecular formula was established as $C_{28}H_{32}O_4$ according to the hydrogen adduct ion peak at *m/z* 433.2368 $[M+H]^+$ (calcd 433.2373), indicating 13 degrees of unsaturation. Absorption bands of carbonyl groups (1710 and 1678 cm^{-1}) and aromatic ring (1450 cm^{-1}) were observed in the IR spectrum. The ^{1}H NMR spectrum (Table 1) exhibited a monosubstituted phenyl [δ_H 7.80 (2H, d, J = 5.6 Hz), 7.53 (1H, t, J = 5.6 Hz), and 7.41 (2H, t, J = 5.6 Hz)] , two olefinic protons [δ_H 5.00 (1H, t, J = 6.4 Hz) and 5.05 (1H, t, J = 6.4 Hz)], and six singlet methyls (δ_H 1.37–1.71). The ^{13}C NMR (Table 1) and HSQC spectra showed 28 carbon signals due to seven quaternary carbons (δ_C 41.8 and 65.3; a non-conjugated ketone at δ_C 207.1; a 1,3-diketone group at δ_C 117.2, 173.2, and 196.9; and an oxygenated carbon at δ_C 91.4), one methine (δ_C 38.1), one methylene (δ_C 27.6), two methyls (δ_C 28.2 and 23.4), and 17 other signals assignable to a benzoyl and two prenyl groups. The aforementioned data showed that 1 is a monocyclic polyprenylated acylphloroglucinol (MPAP) derivative and shares a similar carbon core with that of hypercohin K (Yang et al., 2015). The only difference was the geranyl group at C-5 in hypercohin K was replaced by a prenyl group in 1. The linkage of the C_5 unit (C-14~C-18) was confirmed by the ^{1}H–^{1}H COSY correlation of H_2-14 (δ_H 1.56 and 1.69) with H-15 (δ_H 2.91) and the HMBC correlations from Me-17 (δ_H 1.37)/M-18 (δ_H 1.40) to C-15 (δ_C 38.1) and C-16 (δ_C 91.4)

(Fig. 2). The HMBC correlations from H_2-14 (δ_H 1.69 and 1.56)/H-15 (δ_H 2.91) to C-2 (δ_C 173.2), C-3 (δ_C 41.8), and C-4 (δ_C 207.1) indicated that C-14 and C-15 were directly attached to C-3 to form a cyclopropane moiety. Furthermore, a five-membered ether ring was proposed by the downfield chemical shifts of C-2 (δ_C 173.2) and C-16 (δ_C 91.4). The locations of two prenyl groups were assigned to C-5 by the HMBC cross-peaks from H_2-19 (δ_H 2.65) and H_2-24 (δ_H 2.49 and 2.68) to C-4 (δ_C 207.1), C-5 (δ_C 65.3), and C-6 (δ_C 196.9) (Fig. 2).

The relative configuration of 1 was established by analysis of the ROESY spectrum. The correlation of H-14a (δ_H 1.56)/Me-18 (δ_H 1.40) and H-15 (δ_H 2.91)/Me-17 (δ_H 1.37) defined that CH_2-14 was β-orientated while H-15 was α-orientated (Fig. 5). The electronic circular dichroism (ECD) spectrum of 1 was in good agreement with hypercohin K, whose absolute configurations had been determined as 3*R*, 5*S*, 15*R* by experimental and calculated ECD. Thus, the absolute configurations of 1 were elucidated as 3*R*, 15*R*. (Fig. 7).

Hyperbeanin B (2) gave a molecular formula of $C_{33}H_{40}O_4$ with 14 degrees of unsaturation, as deduced from the HRESIMS ion signal at *m/z* 523.2812 $[M+Na]^+$ (calcd 523.2819). The ^{1}H NMR spectrum (Table 1) showed a monosubstituted benzene [δ_H 7.47 (2H, d, J = 7.5 Hz), 7.44 (2H, t, J = 7.5 Hz), and 7.38 (1H, t, J = 7.5 Hz)], five olefinic protons [δ_H 6.47 (1H, d, J = 9.9 Hz), 5.33 (1H, t, J = 7.1 Hz), 5.27 (1H, d, J = 10.1 Hz), 5.09 (1H, m), and 5.08 (1H, m)], two hydroxy protons (δ_H 12.83 and 6.40), six singlet methyls (δ_H 0.97–1.85). The ^{13}C NMR (Table 1) and HSQC spectra revealed 33 carbon signals, including a carbonyl carbons (δ_C 200.7), two groups of aromatic carbons (δ_C 143.0, 130.1, 127.7 × 2, 127.2 × 2; 162.2, 158.3, 154.7, 105.4, 105.2, 102.0), four pairs of olefinic carbons (δ_C 140.6, 121.8; 136.0, 123.4; 131.5, 124.5; 125.2, 116.1). The aforementioned data indicated 2 is also a MPAP derivative. The HMBC correlations from 2-OH (δ_H 12.83) to C-1 (δ_C 105.4), C-2 (δ_C 162.2), and C-3 (δ_C 105.2), and from 4-OH (δ_H 6.40) to C-3 (δ_C 105.2), C-4 (δ_C 158.3), and C-5 (δ_C 102.0) suggested two hydroxyls were located at C-2 and C-4, respectively (Fig. 2). Combined with the chemical shifts of C-6 (δ_C 154.7) and C-31 (δ_C 77.5), as well as the HMBC correlations from H_3-32 (δ_H 0.97)/H_3-33 (δ_H 0.97) to C-30 (δ_C 125.2) and C-31 (δ_C 77.5), from H-30 (δ_H 5.27) to C-5 (δ_C 102.0), C-31 (δ_C 77.5), C-32 (δ_C 27.5), and C-33 (δ_C 27.5), and from H-29 (δ_H 6.47) to C-4 (δ_C 158.3), C-5 (δ_C 102.0), C-6 (δ_C 154.7), and C-31 (δ_C 77.5) revealed the existence of the unsaturated pyran ring. The assignment of the unsaturated carbon chain at C-3 was further accomplished by the HMBC cross-peaks from H_2-14 (δ_H 3.45) to C-2 (δ_C 162.2), C-3 (δ_C 105.2), C-4 (δ_C 158.3), C-15 (δ_C 121.8), and C-16 (δ_C 140.6).

The HRESIMS data of hyperbeanin C (3) exhibited a positive ion at *m/z* 535.3055 $[M+H]^+$ (calcd 535.3054), suggesting a molecular formula of $C_{33}H_{42}O_6$ with 13 indices of hydrogen deficiency. The ^{1}H NMR spectrum (Table 1) revealed the presence of one monosubstituted benzene [δ_H 7.86 (2H, d, J = 7.0 Hz), 7.52 (1H, t, J = 7.0 Hz), 7.45 (2H, t, J = 7.0 Hz)], one low field proton [δ_H 6.16 (1H, s)], two olefinic protons [δ_H 4.88 (1H, m), 4.86 (1H, m)], and six singlet methyls (δ_H 1.67, 1.66, 1.58, 1.55, 1.39, 1.30). The ^{13}C NMR spectrum (Table 1) combined with HSQC and HMBC indicated 3 is a spirocyclic PPAP with octahydrospiro [cyclohexan-1,5′-indene] core, whose structure is similar to hyperpatulol A (Liu et al., 2019), except that the signals of enolized 1,3-diketone group was absent. The HMBC correlation of H-2 (δ_H 6.16) to C-1 (δ_C 199.8), C-27 (δ_C 179.7), and C-28 (δ_C 133.7) indicated benzoyl group was located at C-2 (Fig. 2). In the ROESY spectrum of 3, the correlations of Me-15 (δ_H 1.39)/H-12 (δ_H 1.93), Me-15 (δ_H 1.39)/H-14b (δ_H 2.63), H-8 (δ_H 1.25)/H-7b (δ_H 2.31), Me-16 (δ_H 1.30)/H-7b (δ_H 2.31), and H-14b (δ_H 2.63)/H-7b (δ_H 2.31) suggested that H-8, H-12, Me-15, and Me-16 were β-oriented (Fig. 5). Moreover, the ROESY interactions of H-2 (δ_H 6.16)/H-14b (δ_H 2.63) revealed that the benzoyl group was at the upper side of the cyclohexane moiety, and H-2 was α-oriented. The ECD spectrum of 3 showed positive cotton effect at 219 nm and negative cotton effects at 252 and 283 nm comparable to those of hyperbeanol F (Fig. 7) (Li et al., 2019). Hence, the absolute configuration of 3 was established as *2R*, *4R*, *8S*, *9R*, *12S*, and *13R*.

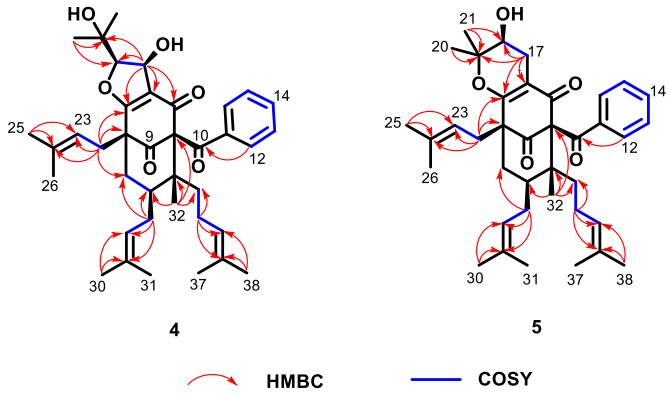


Fig. 3. Key HMBC and ^{1}H–^{1}H COSY correlations of 4–5.

Hyperbeanin D (4) was obtained as colorless oil, and its molecular formula was assigned as $C_{38}H_{50}O_6$ according to the quasi-molecular ion signal at *m/z* 603.3688 $[M+H]^+$ (calcd 603.3680). The 1D and 2D NMR data of 4 were similar to those of hypercohin J with a bicyclo[3.3.1] nonane core (Liu et al., 2013), indicating these two compounds share the same planar structure. This deduction was supported by the HMBC correlations from H_2-22 (δ_H 2.49 and 2.61) to C-4 (δ_C 178.8), C-5 (δ_C 56.0), C-9 (δ_C 205.8), C-23 (δ_C 118.1), and C-24 (δ_C 135.8); from H-17 (δ_H 5.36) to C-2 (δ_C 189.4), C-3 (δ_C 121.0), C-4 (δ_C 178.8), C-18 (δ_C 99.6) and C-19 (δ_C 71.4); and from H-18 (δ_H 4.51) to C-3 (δ_C 121.0), C-4 (δ_C 178.8), C-17 (δ_C 70.8), C-20 (δ_C 25.2), and C-21 (δ_C 24.7) (Fig. 3). Moreover, the chemical shift of C-7 (δc 43.1) and the chemical shift difference between H-6a and H-6b ($\Delta\delta$ ca. 0.39) were in accordance with the classical reported rules (Ciochina and Grossman, 2006), implying that the C-7 substituent was exo. The ROESY correlations of Me-20 (δ_H 1.34)/H-28 (δ_H 4.94) and H-17 (δ_H 5.36)/H-7 (δ_H 1.80), combined with the absence of the correlation on between H-17 (δ_H 5.36) and H-12/H-16 (δ_H 7.55), revealed that H-17 and H-18 were both α-oriented (Fig. 5). Finally, the absolute configuration of 4 was confirmed as *1S, 5R, 7S, 8R, 17S, 18R* by comparison of the ECD spectrum with hyperascyrin C (Hu et al., 2018) (Fig. 7).

Hyperbeanin E (5) gave a molecular formula of $C_{38}H_{50}O_5$ with 14 degrees of unsaturation, as deduced from the HRESIMS ion signal at *m/z* 587.3726 $[M+H]^+$ (calcd 587.3731). Comparison of the NMR data of 5 with those of hyperascyrin J indicated that they are structurally similar, except that the signal for the methyl at C-5 in hyperascyrin J was replaced by a prenyl group (Hu et al., 2018). These deductions were confirmed by the HMBC correlation from H_2-22 (δ_H 2.52) to C-4 (δc 175.8), C-5 (δc 55.5), C-6 (δc 39.4), and C-9 (δc 206.7); from H-17 (δ_H 2.99) to C-3 (δc 118.5), C-4 (δc 175.8), C-18 (δc 93.2), and C-19 (δc 71.9); and from H_3-20 (δ_H 1.33)/H_3-21 (δ_H 1.22) to C-18 (δc 93.2) and C-19 (δc 71.9) (Fig. 3). Likely, the α-orientation of H-7 was elucidated by the chemical shift of C-7 (δc 42.8) and the chemical shift difference between H-6a and H-6b ($\Delta\delta$ ca. 0.51). Moreover, the ROESY correlations of H-17a (δ_H 2.97)/H-12 (δ_H 7.51) and H-18 (δ_H 4.87)/H-17b (δ_H 3.02) revealed H-18 was α-oriented (Fig. 6). The ECD spectrum of 5 resembled that of hyperascyrin J, indicating the absolute configuration of 5 was *1R*, *5R*, *7S*, *8R*, *18S* (Fig. 8).

Hyperbeanin F (6) was obtained as colorless oil. Its molecular formula, $C_{33}H_{42}O_6$, was established by quasi-molecular ion signal at *m/z* 535.3047 $[M+H]^+$ (calcd 535.3054), indicative of 13 indices of hydrogen deficiency. The IR spectrum showed absorption bands for hydroxy (3377 cm^{-1}) and carbonyl groups (1734 and 1695 cm^{-1}). The ^{1}H and ^{13}C NMR spectra (Table 1) of 6 showed high similarity to those of hypersampsone F (Zhang et al., 2016), a homoadamantane type PPAP with a tricyclo[4.3.1.1]undecane core. Further analysis of the 2D NMR spectra of **6** revealed that the only difference of their planar structures arose from the chain at C-5, where the geranyl group in hypersampsone F was replaced by a prenyl group in 6. The chemical shifts of C-25 (δc

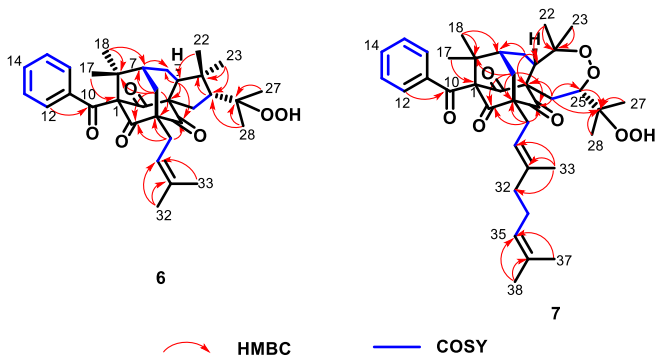


Fig. 4. Key HMBC and ^{1}H–^{1}H COSY correlations of 6–7.

54.5), C-26 (*δc* 85.9), C-27 (*δc* 24.8), and C-28 (*δc* 23.1), along with the HRESIMS data of 6, implied the presence of a peroxide group at C-26. Molecular models indicated that the tetracyclic system established the relative configuration of the chiral centers of C-1, C-3, C-5, and C-7. The ROESY cross-peaks of Me-22 (δ_H 0.93)/H-6a (δ_H 1.89), H-25 (δ_H 2.86)/Me-22 (δ_H 0.93), Me-17 (δ_H 1.46)/H-6b (δ_H 2.52), and H-20 (δ_H 2.06)/Me-18 (δ_H 1.40) were observed, suggesting that H-20 and H-25 were *α*-oriented and *β*-oriented, respectively (Fig. 6). The absolute configuration of 6 was determined to be 1*R*, 3*R*, 5*S*, 7*S*, 20*R*, 25*S* by comparing the experimental ECD spectrum of 6 with that of hypersampsone F (Fig. 8).

The molecular formula of hyperbeanin G (7) was established as $C_{38}H_{50}O_8$ by the signal at *m/z* 635.3578 $[M+H]^+$ (calcd 635.3578) in HRESIMS experiment. Careful analysis of the 2D NMR spectra of 7 indicated the same planar structure as that of hyperisampsin O (Zhu et al., 2016), which possesses a peroxide group and an 1,2-dioxepane functionality (Fig. 4). The relative configuration of 7 was determined by conducting ROESY experiment. The *β*-orientation of H-20 and H-25 were established by the ROESY correlations of Me-17 (δ_H 1.39)/H-6b (δ_H 2.62), H-20 (δ_H 2.60)/H-6a (δ_H 2.15), H-20 (δ_H 2.60)/Me-22 (δ_H 1.29), and H-25 (δ_H 5.33)/Me-22 (δ_H 1.29) (Fig. 6). In addition, the experimental ECD spectrum of 7 was in good agreement with that of hyperisampsin N (Fig. 8) (Zhu et al., 2016), which suggested that the absolute configuration of 7 was 1*R*, 3*R*, 5*S*, 7*S*, 20*R*, 25*R*.

Based on the comparison of their NMR and MS data with the literature values, twenty known PPAPs were identified as 3-farnesyl-2,4,6-trihydroxybenzophenone (8) (Wang and Lee, 2011), hyperbeanal P (9) (Li et al., 2019), hyperbeanal K (10) (Li et al., 2019), hypercohone G (11) (Zhang et al., 2014), hyphenrone T (12) (Liao et al., 2016), hyphenrone V (13) (Liao et al., 2016), furohyperforin (14) (Verotta et al., 1999), sampsonione L (15) (Hu and Sim, 2000), 13,14-didehydroxyguttiferone A (16) (Xu et al., 2019), hypercohin J (17) (Liu et al., 2013), uralodin C (18) (Chen et al., 2010), hyperattenin C (19) (Li et al., 2015), otogirinin D (20) (Ishida et al., 2010), hypersampsonone F (21) (Zhang et al., 2016), hypersampsonone G (22) (Zhang et al., 2016), sampsonione C (23) (Hu and Sim, 1999), plukenetione B (24) (Henry et al., 1999), hyperattenin I (25) (Li et al., 2015), sampsonione F (26) (Hu and Sim, 1999), attenuatumione A (27) (Zhou et al., 2014),

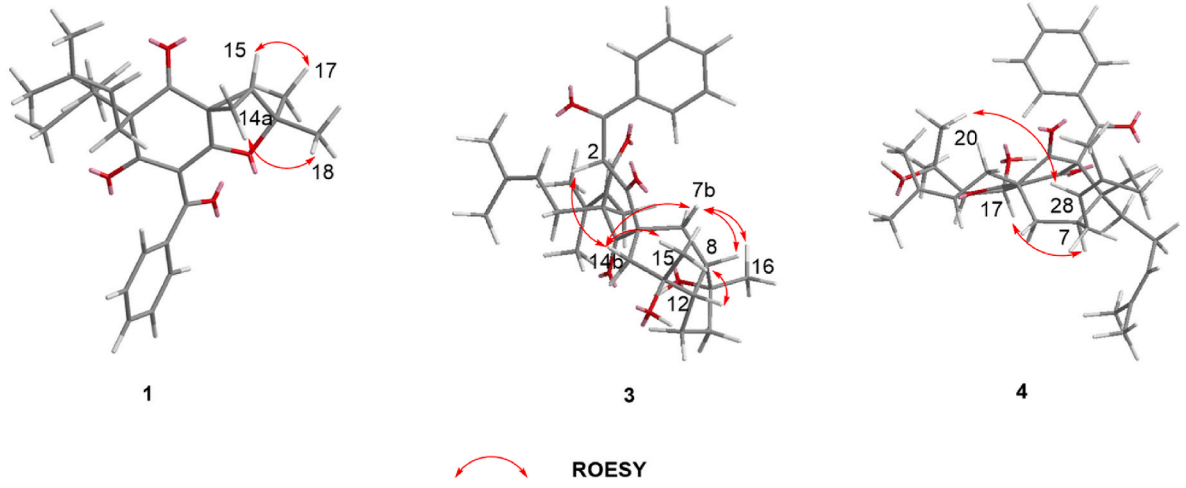


Fig. 5. Key ROESY correlations of 1, 3–4.

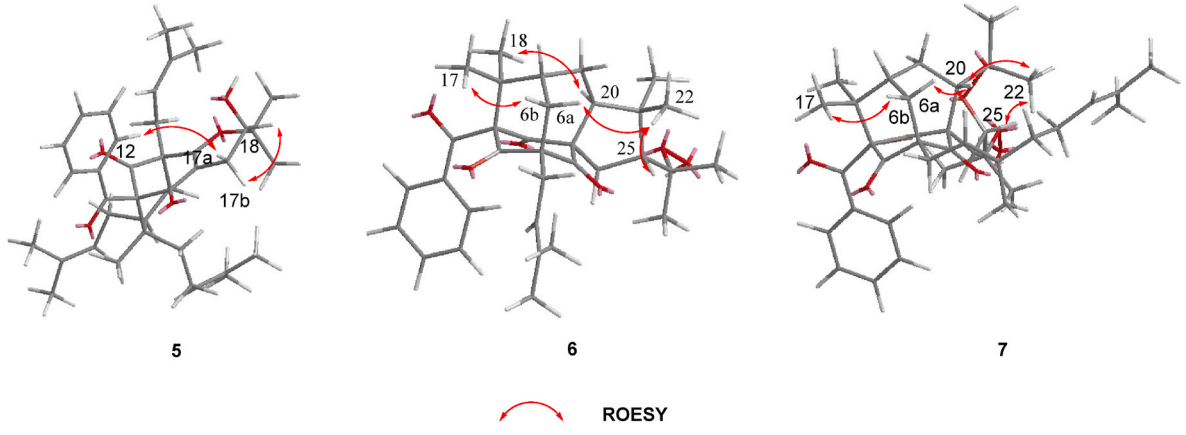


Fig. 6. Key ROESY correlations of 5–7.

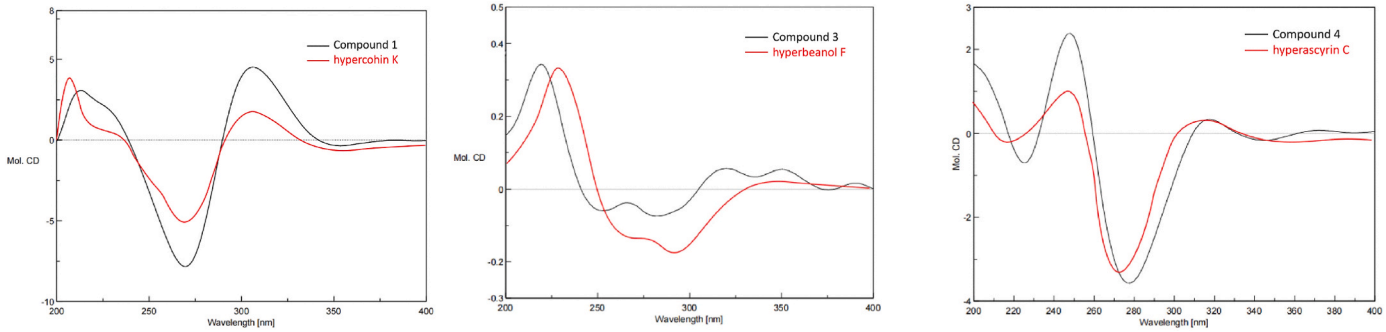


Fig. 7. Experimental ECD spectra of 1, 3–4.

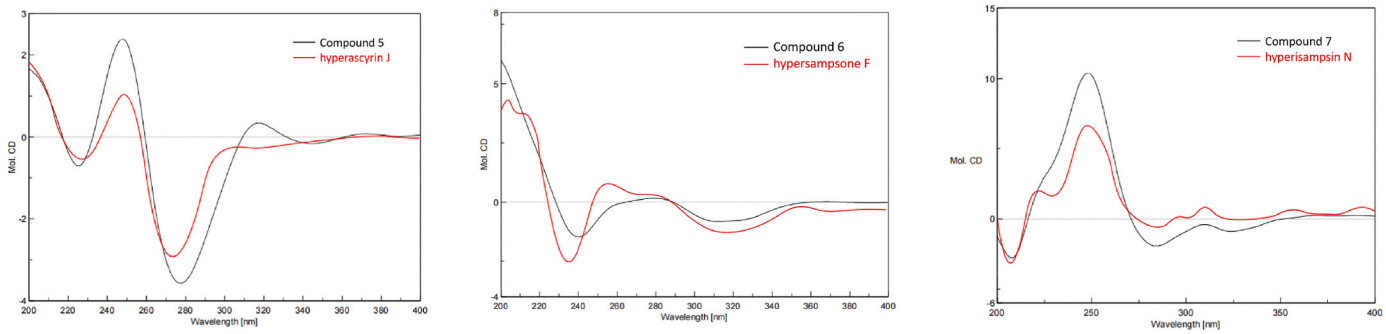


Fig. 8. Experimental ECD spectra of 5–7.

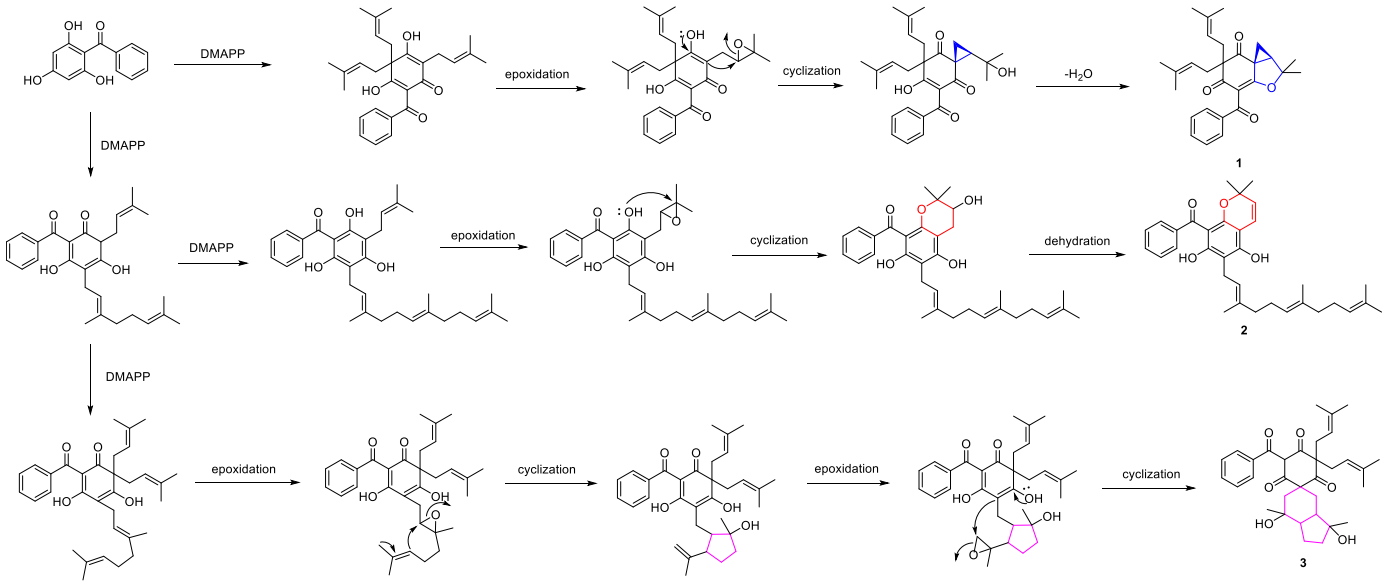


Fig. 9. Plausible biosynthetic pathways of 1–3.

respectively. Some of isolated compounds were evaluated for their hepatoprotective activity against paracetamol-induced HepG2 cell damage. Compared with the positive control bicyclol, compounds 8, 16–18 showed obvious cytoprotection with improving cell viability ranging from 16.70% to 24.41% at 10 μM (Table 3).

Biogenetically, the acylphloroglucinol cores of PPAPs are produced by a characteristic polyketide-type biosynthesis involving the condensation of one acyl-CoA and three malonyl-CoA units. Prenylation of this core moiety affords monocyclic polyprenylated acylphloroglucinols (MPAPs), which may be further cyclized to PPAP-type metabolites with diverse carbon skeletons (Yang et al., 2018). Compound 1 presumably was derived from MPAPs via the cyclization of the C-3 prenyl group to C-3 itself to form a spiro[2.5]octane skeleton, while the spirocyclic core of compound 3 was formed via epoxidation and cyclization of the geranyl group. In addition, compounds 4–7 were probably biosynthesized from the precursors (i-iii) by epoxidation and intramolecular cyclization. The plausible biogenetic pathway for compounds 1–7 is proposed as shown in Fig. 9 and Fig. 10.

3. Conclusions

In conclusion, twenty-seven PPAPs with diverse carbon skeletons

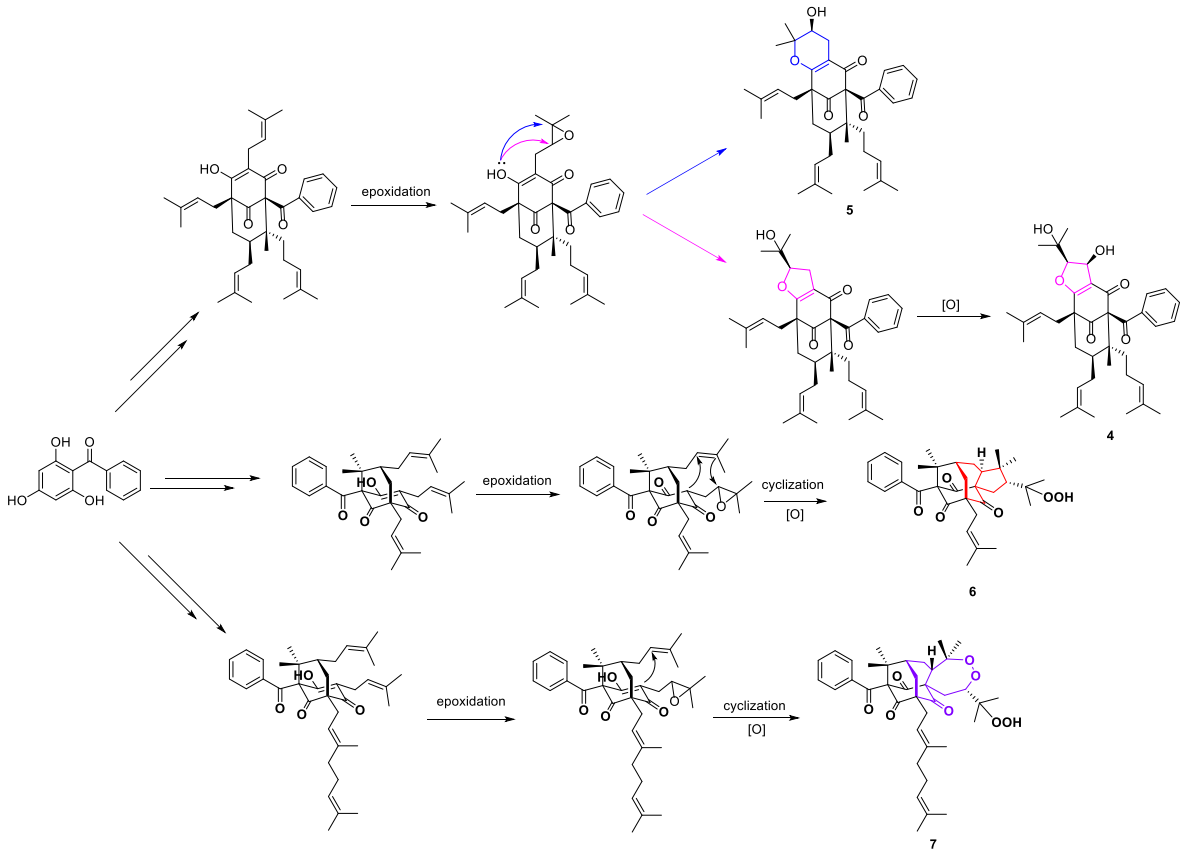


Fig. 10. Plausible biosynthetic pathways of 4–7.

(1–27) were isolated from the ethanol extract of *H. beanii*, including seven new PPAPs hyperbeanin A-G (1–7). Hyperbeanin A (1) is a monocyclic polyprenylated acylphloroglucinols (MPAPs) with an unusual spiro-fused cyclopropane ring. At a concentration of 10 μM, compounds 8, 16–18 showed obvious hepatoprotective activity against paracetamol-induced HepG2 cell damage. This research could provide support for the medical application of *H. beanii* as herbal remedies.

4. Experimental procedures

4.1. General experimental 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 spraying with 10% sulfuric acid in EtOH followed by heating.

4.2. Plant material

The air-dried aerial parts of *Hypericum beanii* N. Robson (Hypericaceae) were purchased from Kunming, Yunnan Province, China (103°3′21″ E, 25°18′43″ N), 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.

4.3. Extraction and isolation

The air-dried aerial parts of *H. beannii* (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 subjected to silica gel CC and eluted with PE/EtOAc (100:0 to 0:100) to gain nine fractions (Fr.1-9). Fr.1 (250.0 g) was fractionated by using diol CC, eluting with PE/EtOAc (100:0 to 0:100) to yield thirteen fractions (Fr.1.1-Fr.1.13). Fr.1.2 (40.0 g) was separated via Sephadex LH-20 CC, eluted with PE/CH_2Cl_2/MeOH (5:5:1) to afford twelve fractions (Fr.1.2.1-Fr.1.2.12). Fr.1.2.1 (2.62 g) was treated with silica gel CC, eluted with PE/EtOAc (20:1 to 4:1), and further purified by preparative HPLC (MeCN/H_2O, 90:10 to 100:0) to yield 24 (5 mg) and 27 (6 mg). Fr.1.2.12 (28.4 g) was subjected to ODS CC, eluted with MeOH/H_2O (80:20 to 100:0), and further purified by preparative HPLC (MeCN/H_2O, 90:10 to 100:0) to yield 20 (12 mg), 23 (9 mg), and 26 (6 mg). Fr.1.5 (14.0 g) was separated via Sephadex LH-20 CC, eluted with PE/CH_2Cl_2/MeOH (5:5:1) to afford six fractions (Fr.1.5.1-Fr.1.5.6). Fr.1.5.4 (489 mg) was purified by preparative TLC with PE/CH_2Cl_2 (2:1) to yield 16 (10.0 mg). Fr.1.6 (5.0 g) was separated via Sephadex LH-20 CC, eluted with PE/CH_2Cl_2/MeOH (5:5:1) to afford three fractions (Fr.1.6.1-Fr.1.6.3). Fr.1.6.3 (760 mg) was further purified by preparative HPLC (MeCN/H_2O, 97:3) to yield 2 (34 mg). Fr.1.7 (14.1 g) was

Table 2
^{1}H NMR and ^{13}C NMR data for compounds 4–5[a], and 7[b].

No	4		5		7	
	δ_H	δ_C	δ_H	δ_C	δ_H	δ_C
1		80.1		79.8		83.4
2		189.4		188.0		206.0
3		121.0		118.5		67.7
4		178.8		175.8		209.0
5		56.0		55.5		70.3
6	1.58 m; 1.96 m	39.1	1.51 m; 2.02 m	39.4	2.14m; 2.62 m	38.2
7	1.80 m	43.1	1.86 m	42.8	2.16 m	44.3
8		50.3		49.9		49.8
9		205.8		206.7		206.2
10		193.6		193.7		194.6
11		136.6		136.9		136.8
12	7.55 d (7.2)	128.6	7.51 d (8.4)	128.3	7.15 d (7.2)	129.7
13	7.29 t (7.2)	128.1	7.26 t (8.4)	128.1	7.34 t (7.2)	129.3
14	7.40 t (7.2)	132.4	7.39 t (8.4)	132.2	7.46 t (7.2)	133.4
15	7.29 t (7.2)	128.1	7.26 t (8.4)	128.1	7.34 t (7.2)	129.3
16	7.55 d (7.2)	128.6	7.51 d (8.4)	128.3	7.15 d (7.2)	129.7
17	5.36 d (3.6)	70.8	2.97 d (11.2); 3.02 d (8.0)	27.3	1.39 s	25.4
18	4.51 d (4.0)	99.6	4.87 dd (10.4, 7.6)	93.2	1.34 s	22.9
19		71.4		71.9	2.00 m; 2.06 m	29.7
20	1.34 s	25.2	1.33 s	26.2	2.60 m	42.6
21	1.31 s	24.7	1.22 s	22.7		89.2
22	2.49 m; 2.61 m	28.6	2.52 d (8.0)	29.5	1.29 s	29.6
23	5.09 t (8.8)	118.1	5.02 m	120.6	1.14 s	20.0
24		135.8		134.9	1.79 dd (14.4, 4.2); 2.91 dd (14.4, 11.4);	32.6
25	1.65 s	25.8	1.69 s	25.8	5.33 dd (10.8, 3.6)	86.1
26	1.69 s	18.2	1.69 s	18.3		85.3
27	1.77 m; 2.13 m	27.4	1.25 m; 1.30 m	31.7	1.27 s	22.7
28	4.94 t (7.2)	122.4	5.00 m	122.5	1.14 s	21.2
29		134.1		133.8	2.56 m; 2.61 m	30.1
30	1.67 s	26.2	1.73 s	25.9	5.27 t (7.2)	120.5
31	1.57 s	17.9	1.59 s	18.2		139.8
32	1.13 s	14.1	1.12 s	14.2	2.03 m	41.1
33	1.59 m; 2.04 m	36.9	1.67 m; 2.07 m	36.7	1.68 s	16.6
34	1.94 m; 2.19 m	25.2	1.96 m; 2.18 m	25.2	2.08 m	27.7
35	5.07 t (7.2)	124.5	5.08 t (6.8)	124.6	5.07 t (7.2)	125.4
36		131.6		131.4		132.3
37	1.65 s	26.0	1.64 s	26.1	1.65 s	26.0
38	1.61 s	18.0	1.62 s	17.9	1.59 s	17.8

[a] Recorded in $CDCl_3$ (^{1}H NMR 400 MHz, ^{13}C NMR 125 MHz).
[b] Recorded in CD_3OD (^{1}H NMR 400 MHz, ^{13}C NMR 125 MHz).

separated via Sephadex LH-20 CC, eluted with PE/CH_2Cl_2/MeOH (5:5:1) to afford eight fractions (Fr.1.7.1-Fr.1.7.8). Fr.1.7.5 (596 mg) was further purified by preparative HPLC (MeCN/H_2O, 90:10 to 95:5) to yield 10 (62 mg). Fr.1.9 (16.7 g) was subjected to ODS CC, eluted with MeOH/H_2O (80:20 to 100:0), and further purified by preparative HPLC (MeCN/H_2O, 90:10 to 100:0) to yield 18 (3 mg). Fr.3 (150.3 g) was fractionated by using MCI CC, eluting with MeOH/H_2O (80:20 to 95:5) to yield nine fractions (Fr.3.1-Fr.3.9). Fr.3.4 (7.2 g) were subjected to ODS CC, eluted with MeOH/H_2O (70:30 to 100:0), and further purified by preparative HPLC (MeOH/H_2O, 92:8 to 96:4) to yield 5 (3 mg) and 9 (10 mg). Fr.3.6 (5.1 g) were subjected to ODS CC, eluted with MeOH/H_2O (70:30 to 100:0), and further purified by preparative HPLC (MeOH/H_2O, 92:8 to 98:2) to yield 14 (9 mg) and 19 (6 mg). Fr.3.8 (18.6 g) were subjected to ODS CC, eluted with MeOH/H_2O (80:20 to 100:0), and further purified by preparative HPLC (MeOH/H_2O, 90:10 to 98:2) to yield 1 (4 mg), 6 (5 mg), 21 (20 mg), and 22 (3 mg). Fr.5 (161.1 g) was fractionated by using MCI CC, eluting with MeOH/H_2O (80:20 to 95:5) to yield ten fractions (Fr.5.1-Fr.5.10). Fr.5.3 (5.6 g) was subjected to ODS CC, eluted with MeOH/H_2O (70:30 to 100:0), and further purified by preparative HPLC (MeOH/H_2O, 90:10 to 95:5) to yield 12 (30 mg), 13 (10 mg), 15 (42 mg), and 25 (4 mg). Fr.5.5 (26.0 g) was subjected to ODS CC, eluted with MeOH/H_2O (70:30 to 100:0), and further purified by preparative HPLC (MeOH/H_2O, 92:8 to 96:4) to yield 8 (794 mg) and 11 (3 mg). Fr.5.7 (10.0 g) was treated with silica gel CC, eluted with PE/EtOAc (9:1 to 1:1), and further purified by preparative HPLC (MeCN/H_2O, 94:10 to 98:2) to yield 4 (5 mg), 7 (2 mg), and 17 (5 mg). Fr.5.9 (10.6 g) was subjected to ODS CC, eluted with MeOH/H_2O (70:30 to 100:0), and further purified by preparative HPLC (MeOH/H_2O, 95:5 to 98:2) to yield 3 (10 mg).

Table 3
Hepatoprotective effects of selected compounds (10 μM) against paracetamol-induced HepG2 cell.[a]

Compound	OD value	Cell viability (% of normal)	Inhibition (% of control)
Normal[b]	1.035 ± 0.067	100.0	
Control[c]	0.568 ± 0.046[d]	54.9	
1	0.493 ± 0.012	47.6	−16.06
2	0.558 ± 0.070	53.9	−2.14
4	0.482 ± 0.012	46.6	−18.42
8	0.659 ± 0.014[e]	63.7	19.49
16	0.682 ± 0.055[e]	65.8	24.41
17	0.674 ± 0.015[e]	65.1	22.70
18	0.646 ± 0.052[f]	62.4	16.70
Bicyclol[g]	0.685 ± 0.097[e]	66.1	25.05

[a] Results are expressed as the means ± SD (n = 3; for normal and control, n = 6).
[b] Normal HepG2 cell.
[c] Paracetamol-induced HepG2 cell.
[d] $P < 0.01$ vs normal.
[e] $P < 0.01$ vs control.
[f] $P < 0.05$ vs control.
[g] Positive control (10 μM).

4.3.1. Hyperbeanin A (1)

Colorless oil; [α] −63.6 (*c* 0.11, MeOH); UV (MeOH) λ_{max} (log ϵ) 203 (4.36) nm, 254 (4.21) nm; ECD (MeOH) λ_{max} (Δε) 213 (+3.05), 269 (−7.85), 306 (+4.49), 353 (−0.37) nm; IR (KBr) ν_{max} 2962, 2924, 1710, 1678, 1630, 1450, 1401 cm^{-1}; ^{1}H and ^{13}C NMR data ($CDCl_3$) see Table 1; HRESIMS *m/z* 433.2368 $[M+H]^+$ (calcd. for $C_{28}H_{33}O_4$, 433.2373).

4.3.2. Hyperbeanin B (2)

Colorless oil; [α] 0 (*c* 0.20, MeOH); UV (MeOH) λ_{max} (log ϵ) 205 (4.16) nm, 294 (3.71) nm, 306 (3.73) nm; IR (KBr) ν_{max} 3372, 2972, 2945, 1640, 1602, 1447 cm^{-1}; ^{1}H and ^{13}C NMR data ($CDCl_3$) see Table 1; HRESIMS *m/z* 523.2812 $[M+Na]^+$ (calcd. for $C_{33}H_{40}O_4Na$, 523.2819).

4.3.3. Hyperbeanin C (3)

Colorless oil; [α] + 34.5 (*c* 0.12, MeOH); UV (MeOH) λ_{max} (log ϵ) 203 (3.92) nm, 246 (3.48) nm, 288 (3.41) nm, 322 (3.38) nm; ECD (MeOH) λ_{max} (Δε) 219 (+0.34), 251 (−0.06), 282 (−0.07), 320 (+0.05), 350 (+0.05) nm; IR (KBr) ν_{max} 3486, 2928, 1769, 1605, 1455 cm^{-1}; ^{1}H and

^{13}C NMR data ($CDCl_3$) see Table 1; HRESIMS *m/z* 535.3055 $[M+H]^+$ (calcd. for $C_{33}H_{43}O_6$, 535.3054).

4.3.4. Hyperbeanin D (4)

Colorless oil; [α] +0.9 (*c* 0.11, MeOH); UV (MeOH) λ_{max} (log ϵ) 203 (7.07) nm, 245 (4.08) nm, 275 (3.96) nm; ECD (MeOH) λ_{max} ($\Delta\varepsilon$) 247 (+6.27), 272 (−5.90), 307 (+1.03) nm; IR (KBr) ν_{max} 3395, 2924, 1725, 1623, 1448, 1381 cm^{-1}; ^1H and ^{13}C NMR data ($CDCl_3$) see Table 2. HRESIMS *m/z* 603.3688 $[M+H]^+$ (calcd. for $C_{38}H_{51}O_6$, 603.3680).

4.3.5. Hyperbeanin E (5)

Colorless oil; [α] −30.0 (*c* 0.10, MeOH); UV (MeOH) λ_{max} (log ϵ) 203 (4.22) nm, 245 (3.88), 284 (3.71) nm; ECD (MeOH) λ_{max} ($\Delta\varepsilon$) 225 (−0.71), 248 (+2.38), 277 (−3.57), 317 (+0.33), 344 (−0.17) nm; IR (KBr) ν_{max} 3370, 2926, 1723, 1621, 1449, 1380 cm^{-1}; ^1H and ^{13}C NMR data ($CDCl_3$) see Table 2; HRESIMS *m/z* 587.3726 $[M+H]^+$ (calcd. for $C_{38}H_{51}O_5$, 587.3731).

4.3.6. Hyperbeanin F (6)

Colorless oil; [α] +10.0 (c 0.11, MeOH); UV (MeOH) λ_{max} (log ϵ) 203 (4.09) nm, 254 (3.74) nm; ECD (MeOH) λ_{max} ($\Delta\varepsilon$) 240 (−1.49), 312 (−0.83) nm; IR (KBr) ν_{max} 3377, 2924, 2854, 1734, 1695, 1449, 1225 cm^{-1}; ^1H and ^{13}C NMR data ($CDCl_3$) see Table 1; HRESIMS *m/z* 535.3047 $[M+H]^+$ (calcd. for $C_{33}H_{43}O_6$, 535.3054).

4.3.7. Hyperbeanin G (7)

Colorless oil; [α] −40.0 (*c* 0.08, MeOH); UV (MeOH) λ_{max} (log ϵ) 203 (4.68) nm, 254 (4.31) nm; IR (KBr) ν_{max} 3382, 2925, 1700, 1449, 1260 cm^{-1}; ECD (MeOH) λ_{max} ($\Delta\varepsilon$) 207 (−2.80), 248 (+10.38), 284 (−1.95), 323 (−0.90) nm; ^1H and ^{13}C NMR data (CD_3OD) see Table 2; HRESIMS *m/z* 635.3578 $[M + H]^+$ (calcd. for $C_{38}H_{51}O_8$, 635.3578).

4.4. Hepatoprotective activity assay

The hepatoprotective effects of the isolated compounds were evaluated 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. Inhibition (%) was obtained by the following formula: Inhibition (%) = [OD (sample)-OD (control)]/[OD (normal)-OD (control)] × 100.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

No data was used for the research described in the article.

Acknowledgments

This work was financially supported by Projects of INTERNATIONAL COOPERATION and Exchanges NSFC (NSFC-VR, No. 81361138020); International Cooperation Project of Qinghai Province (2020-HZ-803); and CAMS Innovation Fund for Medical Sciences (CIFMS, no. 2021-I2M-1–028). Shenyang Young and Middle-aged Scientific and Technological Innovation Talents Support Plan (RC210485).

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.phytochem.2022.113413.

References

Chen, X.Q., Li, Y., Cheng, X., Wang, K., He, J., Pan, Z.H., Li, M.M., Peng, L.Y., Xu, G., Zhao, Q.S., 2010. Polycyclic polyprenylated acylphloroglucinols and chromone *O*-glucosides from *Hypericum henryi* subsp. *uraloides*. Chem. Biodivers. 7, 196–204. https://doi.org/10.1002/cbdv.200900009.

Chen, X.Q., Li, Y., Li, K.Z., Peng, L.Y., He, J., Wang, K., Pan, Z.H., Chen, X., Li, M.M., Zhao, Q.S., Xu, G., 2011. Spirocyclic acylphloroglucinol derivatives from *Hypericum beanii*. Chem. Pharm. Bull. 59, 1250–1253. https://doi.org/10.1248/cpb.59.1250.

Ciochina, R., Grossman, R.B., 2006. Polycyclic polyprenylated acylphloroglucinols. Chem. Rev. 106, 3963–3986. https://doi.org/10.1021/cr0500582.

Editorial Committee of the Administration Bureau of Traditional Chinese Medicine, 1999. Chinese Materia Medica (Zhonghua Bencao). Shanghai Science and Technology Press, Shanghai.

Guo, Y., Zhang, N., Chen, C.M., Huang, J.F., Li, X.N., Liu, J.J., Zhu, H.C., Tong, Q.Y., Zhang, J.W., Luo, Z.W., Xue, Y.B., Zhang, Y.H., 2017. Tricyclic polyprenylated acylphloroglucinols from st John's wort, *Hypericum perforatum*. J. Nat. Prod. 80, 1493–1504. https://doi.org/10.1021/acs.jnatprod.6b01178.

Henry, G.E., Jacobs, H., Carrington, C.M.S., Mclean, S., Reynolds, W.F., 1999. Prenylated benzophenone derivatives from caribbean clusia species (guttiferae). Plukenetiones B-G and xerophenone A. Tetrahedron 55, 1581–1596. https://doi.org/10.1016/S0040-4020(98)01203-4.

Hu, L.H., Sim, K.Y., 1999. Sampsoniones C-H, a unique family of polyprenylated benzophenone derivatives with the novel tetracydo[7.3.1.1^{3,11}.0^{3,7}]tetradecane-2,12,14-trione skeleton, from *Hypericum sampsonii*(Guttiferae). Tetrahedron Lett. 40, 759–762. https://doi.org/10.1016/S0040-4039(98)02366-1.

Hu, L.H., Sim, K.Y., 2000. Sampsoniones A-M, a unique family of caged polyprenylated benzoylphloroglucinol derivatives, from *Hypericum sampsonii*. Tetrahedron 56, 1379–1386. https://doi.org/10.1016/S0040-4020(00)00010-7.

Hu, J.W., Shi, M.J., Wang, J.J., Li, L., Jiang, J.D., Ji, T.F., 2018. Methylated polycyclic polyprenylated acylphloroglucinol derivatives from Hypericum ascyron. J. Nat. Prod. 81, 2348–2356. https://doi.org/10.1021/acs.jnatprod.8b00176.

Ishida, Y., Shirota, O., Sekita, S., Someya, K., Tokita, F., Nakane, T., Kuroyanagi, M., 2010. Polyprenylated benzoylphloroglucinol-type derivatives including novel cage compounds from *Hypericum erectum*. Chem. Pharm. Bull. 58, 336–343. https://doi.org/10.1248/cpb.58.336.

Li, D.Y., Xue, Y.B., Zhu, H.C., Li, Y., Sun, B., Liu, J.J., Yao, G.M., Zhang, J.W., Du, G., Zhang, Y.H., 2015. Hyperattenins A-I, bioactive polyprenylated acylphloroglucinols from *Hypericum attenuatum* Choisy. RSC Adv. 5, 5277–5287. https://doi.org/10.1039/C4RA11675E.

Li, Y.R., Xu, W.J., Wei, S.S., Lu, W.J., Luo, J., Kong, L., 2019. Y. Hyperbeanols F-Q, diverse monoterpenoid polyprenylated acylphloroglucinols from the flowers of *Hypericum beanii*. Phytochemistry 159, 56–64. https://doi.org/10.1016/j.phytochem.2018.12.005.

Li, W.X., Xu, W.J., Luo, J., Yang, L., Kong, L.Y., 2021. Type B polycyclic polyprenylated acylphloroglucinols from the roots of *Hypericum beanii*. Chin. J. Nat. Med. 19, 385–390. https://doi.org/10.1016/S1875-5364(21)60037-7.

Liao, Y., Yang, S.Y., Li, X.N., Yang, X.W., Xu, G., 2016. Polyprenylated acylphloroglucinols from the fruits of *Hypericum henryi*. Sci. China Chem. 59, 1216–1223. https://doi.org/10.1007/s11426-016-0052-4.

Liu, X., Yang, X.W., Chen, C.Q., Wu, C.Y., Zhang, J.J., Ma, J.Z., Wang, H., Yang, L.X., Xu, G., 2013. Bioactive polyprenylated acylphloroglucinol derivatives from Hypericum cohaerens. J. Nat. Prod. 76, 1612–1618. https://doi.org/10.1021/np400287r.

Liu, Y.Y., Ao, Z., Xu, Q.Q., Zhu, D.R., Chen, C., Wang, X.B., Luo, J.G., Kong, L.Y., 2019. Hyperpatulols A-I, spirocyclic acylphloroglucinol derivatives with antimigration activities from the flowers of Hypericum patulum. Bioorg. Chem. 87, 409–416. https://doi.org/10.1016/j.bioorg.2019.03.025.

Nürk, N.M., Madriñán, S., Carene, M.A., Chase, M.W., Blattner, F.R., 2013. Molecular phylogenetics and morphological evolution of St: John's wort (*Hypericum*; Hypericaceae). Mol. Phylogenet 1, 1–16. https://doi.org/10.1016/j.ympev.2012.08.022.

Raso, G.M., Pacilio, M., Carlo, G.D., Esposito, E., Pinto, L., Meli, R., 2002. In vivo and in vitro anti-inflammatory effect of *Echinacea purpurea* and *Hypericum perforatum*. J. Pharm. Pharmacol. 54, 1379–1383. https://doi.org/10.1211/002235702760345464.

Richard, J.A., Pouwer, R.H., Chen, Y.K., 2012. The chemistry of the polycyclic polyprenylated acylphloroglucinols. Angew. Chem. Int. Ed. 51, 4536–4561. https://doi.org/10.1002/anie.201103873.

Saddiqe, Z., Naeem, I., Maimoona, A., 2010. A review of the antibacterial activity of *Hypericum perforatum* L. J. Ethnopharmacol. 131, 511–521. https://doi.org/10.1016/j.jep.2010.07.034.

Shiu, W.K.P., Gibbons, S., 2006. Anti-staphylococcal acylphloroglucinols from *Hypericum beanii*. Phytochemistry 67, 2568–2572. https://doi.org/10.1016/j.phytochem.2006.09.037.

Silva, B.A., Ferreres, F., Malva, J.O., Dias, A.C.P., 2005. Phytochemical and antioxidant characterization of *Hypericum perforatum* alcoholic extracts. Food Chem. 90, 157–167. https://doi.org/10.1016/j.foodchem.2004.03.049.

Suo, X.Y., Liu, X.Y., Liu, X.W., Li, X.X., Zhu, T.T., Ji, T.F., Liu, B., 2021. Four new polyprenylated acylphloroglucinol derivatives from *Hypericum beanii*. J. Asian Nat. Prod. Res. 30, 1–10. https://doi: 10.1080/10286020.2021.2016716.

Tian, D.S., Yi, P., Xia, L., Xiao, X., Fan, Y.M., Gu, W., Huang, L.J., Ben-David, Y., Di, Y.T., Yuan, C.M., Hao, X.J., 2016. Garmultins A−G, biogenetically related polycyclic acylphloroglucinols from *Garcinia multiflora*. Org. Lett. 18, 5904–5907. https://doi.org/10.1021/acs.orglett.6b03004.

Verotta, L., Appendino, G., Belloro, E., Jakupovic, J., Bombardelli, E., 1999. Furohyperforin, a prenylated phloroglucinol from St. John's Wort (*Hypericum perforatum*). J. Nat. Prod. 62, 770–772. https://doi.org/10.1021/np980470v.

Verotta, L., 2002. Are acylphloroglucinols lead structures for the treatment of degenerative diseases? Phytochemistry Rev. 1, 389–407. https://doi.org/10.1023/A:1026069624278.

Wang, X., Lee, Y.R., 2011. Efficient synthesis of polycycles bearing prenylated, geranylated, and farnesylated citrans: application to 3′-prenylrubranine and petiolin D regioisomer. Tetrahedron 67, 9179–9184. https://doi.org/10.1016/j.tet.2011.09.075.

Whiskey, E., Werneke, U., Taylor, D., 2001. A systematic review and meta-analysis of *Hypericum perforatum* in depression: a comprehensive clinical review. Int. Clin. Psychopharmacol. 16, 239–252. https://doi.org/10.1097/00004850-200109000-00001.

Xu, W.J., Tang, P.F., Lu, W.J., Zhang, Y.Q., Wang, X.B., Zhang, H., Luo, J., Kong, L.Y., 2019. Hyperberins A and B, type B polycyclic polyprenylated acylphloroglucinols with bicyclo[5.3.1]hendecane core from *Hypericum beanii*. Org. Lett. 21, 8558–8562. https://doi.org/10.1021/acs.orglett.9b03098.

Yang, X.W., Yang, J., Liao, Y., Ye, Y., Li, Y.P., Yang, S.Y., Xia, F., Xu, G., 2015. Hypercohin K, a polycyclic polyprenylated acylphloroglucinol with an unusual spiro-fused cyclopropane ring from *Hypericum cohaerens*. Tetrahedron Lett. 56, 5537–5540. https://doi.org/10.1016/j.tetlet.2015.08.033.

Yang, X.W., Grossman, R.B., Xu, G., 2018. Research progress of polycyclic polyprenylated acylphloroglucinols. Chem. Rev. 118, 3508–3558. https://doi.org/10.1021/acs.chemrev.7b00551.

Zhang, J.J., Yang, X.W., Ma, J.Z., Liu, X., Yang, L.X., Yang, S.C., Xu, G., 2014. Hypercohones D-G, New polycyclic polyprenylated acylphloroglucinol type natural products from *Hypericum cohaerens*. Nat. Prod. Bioprospect. 4, 73–79. https://doi.org/10.1007/s13659-014-0007-5.

Zhang, J.S., Zou, Y.H., Guo, Y.Q., Li, Z.Z., Tang, G.H., Yin, S., 2016. Polycyclic polyprenylated acylphloroglucinols: natural phosphodiesterase-4 inhibitors from *Hypericum sampsonii*. RSC Adv. 58, 53469–53476. https://doi.org/10.1039/C6RA08805H.

Zhou, Z.B., Zhang, Y.M., Pan, K., Luo, J.G., Kong, L.Y., 2014. Cytotoxic polycyclic polyprenylated acylphloroglucinols from Hypericum attenuatum. Fitoterapia 95, 1–7. https://doi.org/10.1016/j.fitote.2014.02.011.

Zhu, H.C., Chen, C.M., Zhang, J.W., Guo, Y., Tan, D.D., Wei, G.Z., Yang, J., Wang, J.P., Luo, Z.W., Xue, Y.B., Zhang, Y.H., 2016. Hyperisampsins N and O, two new benzoylated phloroglucinol derivatives from *Hypericum sampsonii*. Chin. Chem. Lett. 28, 986–990. https://doi.org/10.1016/j.cclet.2016.11.014.