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Choushenosides A-C, three dimeric catechin glucosides from *Codonopsis pilosula* collected in Yunnan province, China

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ABSTRACT

Choushenosides A-C, three dimeric catechin glucosides, were isolated from the roots of *Codonopsis pilosula* cultivated at high elevations in Yunnan province of the People's Republic of China. The structures of these substances were determined by using spectroscopic and chemical methods. Biological evaluation showed that choushenoside C is a dose-dependent inhibitor of SIRT1.

1. Introduction

Specialized metabolites are synthesized by metabolic pathways, which in turn are regulated by congenital and acquired factors. A consensus has been reached that the nature of specialized metabolites in plants is dependent on the growing environment. Actually, this dependence is also seen with microorganisms where it is widely observed that one strain could produce many different compounds (OSMAC) in a culture condition dependent manner (Jiang et al., 2016a,b). *Codonopsis pilosula* (Franch.) Nannf. (Campanulaceae) is a perennial plant that grows at altitudes of 1500–3000 m in the People's Republic of China. Previous studies revealed that this plant contains phytosteroids, sesquiterpenes, triterpenes, alkaloids, alkylalcohol glycosides, phenylpropanoid glycosides, polyacetylene glycosides, neolignan, and polysaccharides (Yang et al., 2013). The roots of *C. pilosula*, known as Dang Shen in Chinese, are a common traditional Chinese medicine used for the treatment of Qi deficiency. The results of pharmacological investigations showed that the extract of *C. pilosula* regulates immunity, improves learning and memory, and inhibits iNOS (Jiang et al., 2016a,b; Jiang et al., 2015). In a recent study of traditional Chinese medicines, we explored *C. pilosula*, a herb locally known as Chou Shen, which is mainly found in Yunnan province. Local inhabitants of this area have utilized the fresh roots of this plant as a vegetable for soup making for many years even though its consumption causes the frequent release of anal gases. This phenomenon is not associated with the use of Dang Shen that is produced in northwest of China, which belongs to the same species as does *C. pilosula*. This difference attracted our attention and served as the basis of a study on Chou Shen aimed at gaining insight into differences that exist between *C. pilosula* grown in different regions and paving the way for developing Chou Shen as a healthcare food. Below, we describe the results of this effort, which led to the isolation, structural identification and biological evaluation of three novel catechin dimers **1–3**.

2. Results and discussion

2.1. Isolation and structure elucidation of 1–3

The EtOH extract of *C. pilosula* was partitioned between water and EtOAc. The aqueous layer was concentrated in vacuo giving a residue that was subjected to a chromatography protocol to produce **1–3**.

Choushenoside A (**1**) was isolated as a brown yellow powder. The ^{13}C NMR and DEPT spectra (Table 1) of **1** contain 22 carbon resonances attributed to three methylene (one oxygenated), eleven methine (four sp^2, seven oxygenated sp^3), and eight quaternary carbons (all sp^2 including five oxygenated). The ^{1}H NMR spectrum of this substance contains signals at δ_H 3.95 (d, J = 8.3 Hz, H-2), 3.68 (m, H-3), 2.86 (dd, J = 16.0, 5.8 Hz, Ha-4), and 2.41 ppm (dd, J = 16.0, 9.4 Hz, Hb-4). In

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Table 1
^{1}H (600 MHz) and^{13}C NMR (150 MHz) data of **1** in methanol-d_4 (δ in ppm, J in Hz).

Position	δ_H	δ_C	Position	δ_H	δ_C
2, 2‴	3.95, d (8.3)	82.5 CH	3′, 3‴′		145.9 C
3, 3‴	3.68, m	69.1 CH	4′, 4‴′		146.0 C
4, 4‴	2.86, dd (16.0, 5.8) 2.41, dd (16.0, 9.4)	27.9 CH_2	5′, 5‴′	6.70, d (8.1)	116.2 CH
5, 5‴		155.1 C	6′, 6‴′	6.70, br.d (8.1)	120.5 CH
6, 6‴		111.0 C	1″, 1‴″	4.72, d (7.8)	101.7 CH
7, 7‴		155.4 C	2″, 2‴″	3.56, t (8.1)	74.4 CH
8, 8‴	6.19, s	94.6 CH	3″, 3‴″	3.39, overlap	77.9 CH
9, 9‴		154.3 C	4″, 4‴″	3.39, overlap	71.4 CH
10, 10‴		103.5 C	5″, 5‴″	3.39, overlap	77.8 CH
1′, 1‴′		132.5 C	6″, 6‴″	3.91, d (12.0) 3.74, dd (12.0, 4.4)	62.4 CH_2
2′, 2‴′	6.66, d (1.6)	115.9 CH	CH_2	3.86, s	18.1 CH_2

addition, an ABX spin pattern [δ_H 6.66 (d, J = 1.6 Hz, H-2′), 6.70 (d, J = 8.1 Hz, H-5′), 6.70 (brd, J = 8.1 Hz, H-6′)] is observed in this spectrum. Moreover, the spectrum contains resonances in the mid-field region, which are characteristic of protons in a sugar moiety, along other diagnostic signals that are similar to those of catechin-7-*O*-*β*-D-glucoside (**1a**) (Foo and Karchesy, 1989). These findings suggest that **1** is a glucoside containing catechin. The major difference between the spectra of **1a** and **1** is that the resonance for H-6 of **1a** is absent from the spectrum of **1**, being replaced by a methylene signal associated with a group that is attached to C-6. This conclusion is demonstrated by observation of HMBC correlations (Fig. 2) of C$\underline{H_2}$/C-5, C-6, C-7. In addition, HMBC correlations of H-1″/C-7 and C$\underline{H_2}$/C-5, C-6, C-7 indicate the position of attachment of the sugar moiety.

At this point in the analysis, all NMR resonances can be fully assigned by using 2D NMR. However, characterization of the remaining CH_2 group at C-6 is ambiguous because the ^{1}H NMR signal at 3.86 ppm suggests that the methylene carbon is attached to oxygen whereas the significantly upfield 18.1 ppm ^{13}C NMR chemical shift of the carbon in this group is not consistent with this conclusion. A solution to this problem is found by assigning the structure of **1** to be a symmetric dimer of a catechin derivative. To gain evidence for this possibility, the HRMS of **1** was analyzed. The results show that the spectrum contains a quasimolecular ion peak at m/z 939.2521 $[M+Na]^+$ associated with the molecular formula $C_{43}H_{48}O_{22}$. This finding led to assignment of the planar structure of **1**. The *trans* relationship of H-2/H-3 in this substance was readily ascertained on the basis of 8.3 Hz coupling constant in the doublet for H-2.

To assign the absolute configuration of the sugar moiety in **1**, acid hydrolysis was carried out. TLC and GC analysis showed that this process generates D-glucose. Specifically, L-cysteine methyl ester hydrochloride derivatives of D- and L-glucose were prepared and compared to that of the product formed by similar treatment of **1** by using GC. The retention time for the L-cysteine methyl ester hydrochloride derivative arising from **1** is 21.147 min, which is closer to that of D-glucose (21.081 min) rather than that of L-glucose (21.615 min).

Choushenoside B (**2**), obtained as a brown yellow powder, has the molecular formula $C_{43}H_{48}O_6$ (20 degrees of unsaturation), based on analysis of its HRESIMS, ^{13}C NMR and DEPT spectra. The ^{13}C NMR and DEPT spectra show that this substance contains 43 carbons including five methylene (two oxygenated), twenty-two methine (eight olefinic and fourteen aliphatic), and sixteen quaternary carbons (sixteen olefinic including eight oxygenated). Data for **1** and the appearance of

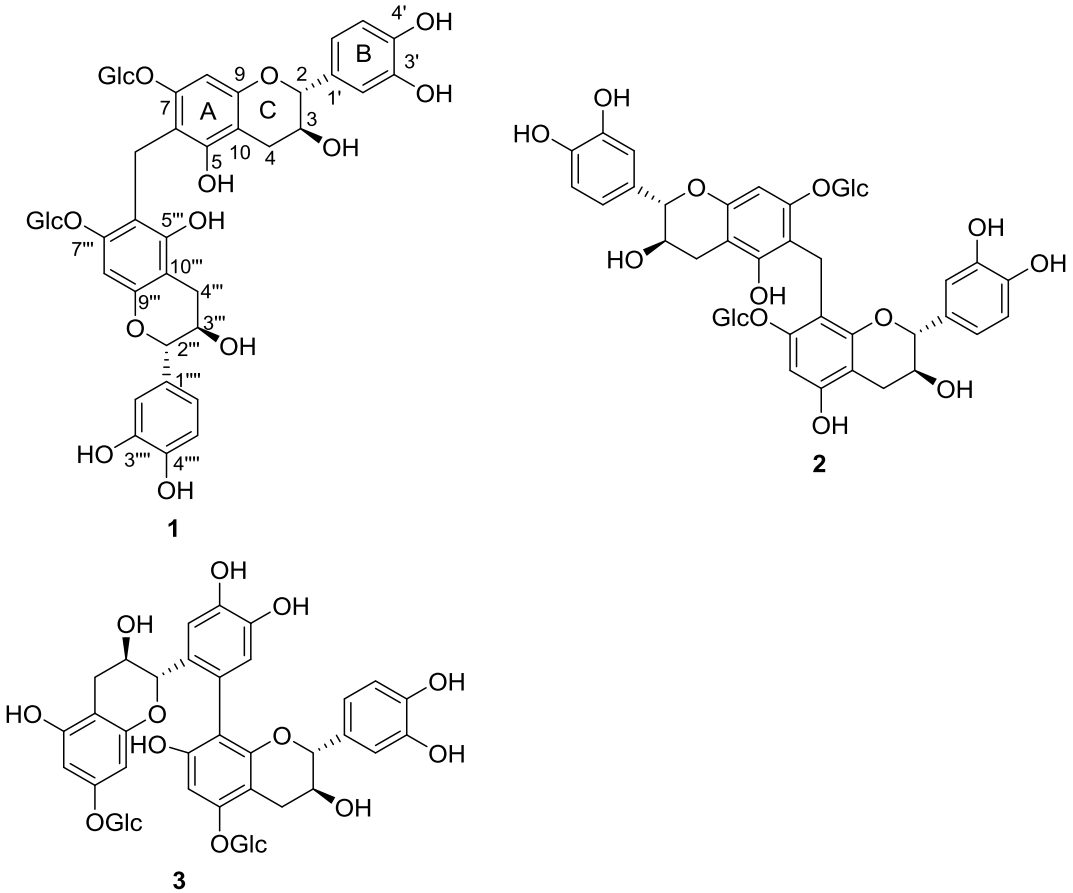

Fig. 1. The structures of catechin dimer glucosides **1–3** from *Codonopsis pilosula*.

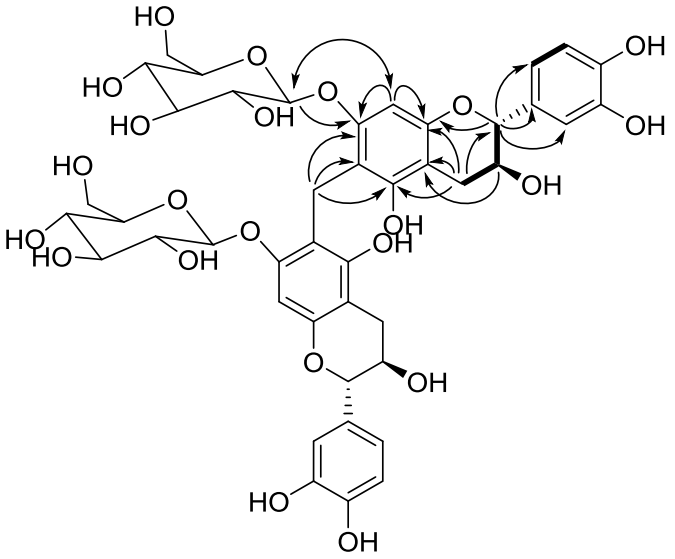

Fig. 2. Key ^{1}H-^{1}H COSY (—), HMBC (⤳), and ROESY (⤳) correlations for **1**.

pairs of peaks in its NMR spectra led us to conclude that **2** is also a dimer of a catechin derivative. Actually, the observation of ^{1}H-^{1}H COSY correlations (Fig. 3, bold lines) of H-2/H-3/H-4, H-2‴/H-3‴/H-4‴ and the presence of diagnostic signals for two ABX spin systems (H-2′, H-3′, H-4′; H-2‴, H-3‴, H-4‴) confirmed this conclusion. Thus, the structure of **2** is similar to that of **1** differing only in the connection of the two catechin glycosides. Specifically, HMBC correlations of C$\underline{H}_2$/C-5‴, C-9, H-6/C-5, C-10 show that C-8 in **2** is linked with C-6‴ via a methylene carbon. In addition, the presence of HMBC correlations of H-1″/C-7 and H-1⁗/C-7‴ clearly indicates the locations of two sugar moieties in the planar structure of **2** and, similarly, the $J_{H\text{-}2,H\text{-}3}$ (7.3 Hz) and $J_{H\text{-}2‴,H\text{-}3‴}$ (7.9 Hz) values indicate the presence of two *trans* relationships (Fig. 1). Finally, evidence for the presence of a D-glucose residue in **2** comes from analysis of the acid hydrolysis product carried out in the same manner as described for **1**.

Choushenoside C (**3**), obtained as a brownish yellow powder, has the molecular formula $C_{42}H_{46}O_6$ (20 degrees of unsaturation), based on analysis of its HRESIMS, ^{13}C NMR and DEPT spectra. The ^{13}C NMR and DEPT spectra, along with the results of HSQC experiments, show that this substance contains 42 carbons including four methylene (two oxygenated), twenty-two methine (eight olefinic and fourteen aliphatic), and sixteen quaternary carbons (sixteen olefinic including eight oxygenated). The ^{1}H, ^{13}C NMR resonances of **3** appear as pairs and resemble those in the spectra of **2**. The difference between the structures of **2** and **3** is that the two glycoside groups in the latter substance are connected via C-8 and C-6⁗ based on the observations of correlations H-5⁗/C-6⁗, C-1⁗, C-8, H-6/C-5, C-10, and H-3/C-10 (Fig. 4). In addition, the existence of glycoside groups at C-5 and C-7‴ in **3** is supported by HMBC correlations of H-1″/C-5 and H-1⁗/C-7‴. The coupling constants for H-2 (J = 6.2 Hz) and H-2‴ (J = 5.7 Hz) indicate that two *trans* relationships are present in the pyran rings in **3**. Finally, evidence for the presence of the D-glucose moiety in **3** also comes from analysis of the acid hydrolysis product formed in the manner described for **1**.

2.2. Biological evaluation

The nicotinamideadenosine dinucleotide (NAD)-dependent deacetylase SIRT1 regulates a wide range of cellular functions and is implicated in many diseases such as those derived from aging, cancer, neurodegeneration, metabolic and immune malfunctions (Mvunta et al., 2017; Cho and Dai, 2016; Ma and Li, 2015; Luo et al., 2014; Cao et al., 2016; Zhang et al., 2017). Considering the fact that traditional applications of Chou Shen are associated with aging, the inhibitory activities of **1–3** against SIRT1 were determined. The results show that only **3** is an inhibitor of SIRT1. (Fig. 5), and that **1** and **2** are not active even at concentrations as high as 200 μM. Owing to the differences between the structure of **3** and those of **1** and **2**, it can be proposed that dimerization through rings A and B is important feature for SIRT1 inhibitory activity.

3. Conclusions

To conclude, three undescribed catechin glucosides were isolated from *Codonopsis pilosula* roots and structurally identified. Biological evaluations revealed that choushenoside C is a SIRT1 inhibitor. This study not only sets the foundation for developing *C. pilosula* as a healthcare food for the prevention of SIRT1-associated disorders, but it also suggests that choushenoside C might be a potent structural template worth further optimization as a SIRT1 inhibitor.

4. Experimental

4.1. General experimental procedures

Column chromatography was undertaken on D101 macroporousresin (Tianjin Haiguang Chemical Co., Ltd., People's Republic of China), RP-18 (40–60 μm; Daiso Co., Japan), and Sephadex LH-20 (Amersham Pharmacia, Sweden). Optical rotations were collected on a Horiba SEPA-300 polarimeter. UV spectra were obtained on a Shimadzu UV-2401PC spectrometer. CD spectra were measured on a Chirascan instrument. GC analysis was performed using an Agilent 6890N gas chromatography instrument. Semi-preparative or analytic HPLC was carried out using an Agilent 1200 liquid chromatograph, the column used was a 250 mm × 9.4 mm, i.d., 5 μm. NMR spectra were recorded on a Bruker AV-400 or an AV-600 spectrometer with TMS as an internal standard. ESIMS and HRESIMS were collected by an Agilent G6230TOF MS spectrometer.

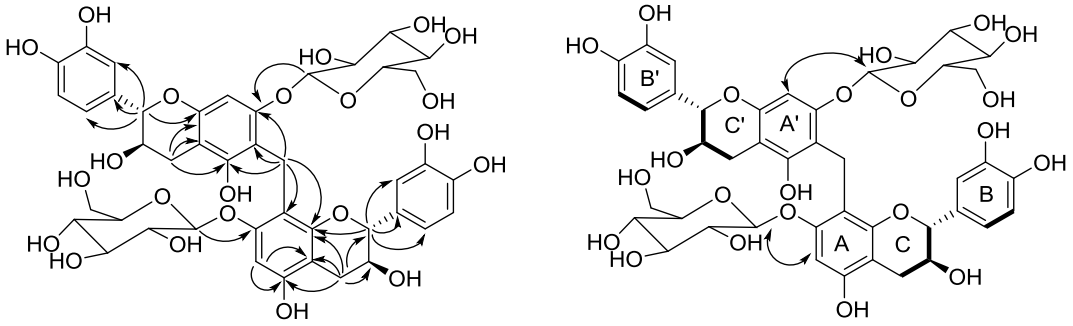

Fig. 3. Key ^{1}H-^{1}H COSY (—), HMBC (⤳), and ROESY (⤳) correlations for **2**.

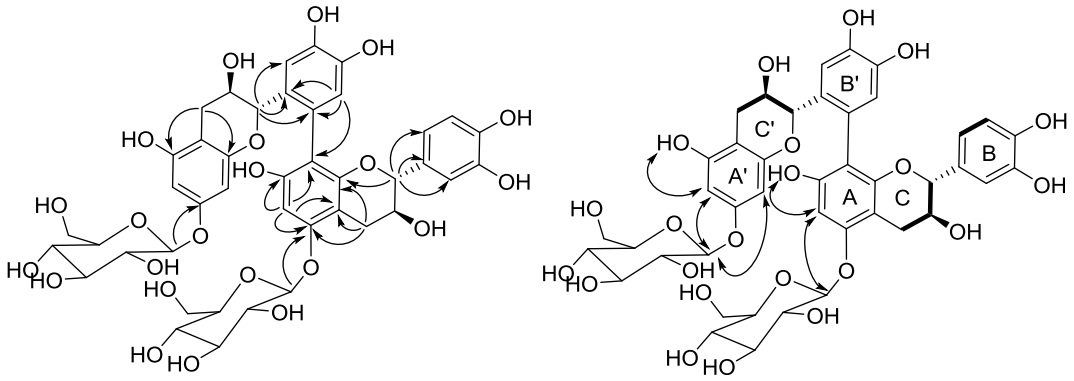

Fig. 4. Key ^{1}H-^{1}H COSY (▬), HMBC (⌒), and ROESY (⌒) correlations for **3**.

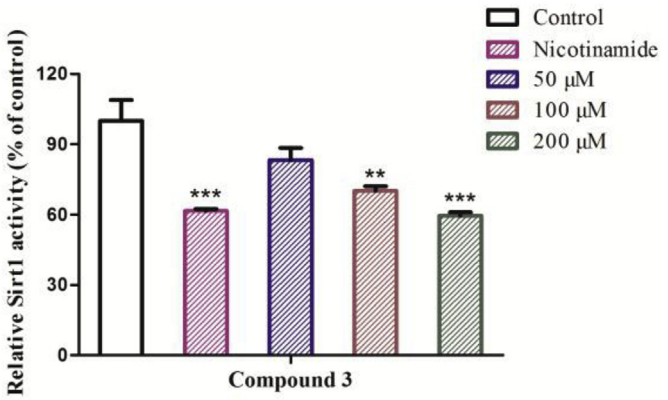

Fig. 5. Effects of compound **3** on SIRT1 activity. SIRT1 enzyme activity was measured using a SIRT1 Fluorometric Drug Discovery Kit. The results are presented as the percentage of activity relative to the control in each group. Statistical analysis was performed using one-way analysis of the variance (ANOVA) followed by Bonferroni's multiple comparison tests. $^{**}p < 0.01$, $^{***}p < 0.001$ indicates significant differences between control and treatment groups.

4.2. Plant material

The roots of *Codonopsis pilosula* (Franch.) Nannf. (Campanulaceae) were collected from Jinyuan of Xundian County (25°91′ N, 103°14′ E) in Yunnan province, People's Republic of China, a cultivation base, in November, 2015. The material cultivated at this site was previously identified by Prof. De-Yuan Hong at Beijing Institute of Botany, Chinese Academy of Sciences, People's Republic of China, and a voucher specimen (1016268) was deposited at the Herbarium of Kunming Institute of Botany, Chinese Academy of Sciences, People's Republic of China.

4.3. Extraction and isolation

The dried roots of *C. pilosula* (20 kg) were powdered and soaked in 85% aqueous EtOH (4 × 80 L × 24 h) to give a crude extract, which was suspended in water followed by extraction with EtOAc to afford an EtOAc soluble extract and an aqueous extract. The latter was divided into three parts (Fr.1–Fr.3) by using a D101 macroporous resin column eluted with an aqueous EtOH gradient (5%, 40%, and 100%). Fr.2 (30 g) was separated by using Sephadex LH-20 (MeOH) to yield two fractions (Fr.2.1 and Fr.2.2). Fr.2.2 (19 g) was further separated by using RP-18 column (MeOH/H_2O, 10%–70%) to give eight fractions (Fr.2.2.1–Fr.2.2.8). Of which, Fr.2.2.2 (2.3 g) was subjected to Sephadex LH-20 (MeOH) followed by semi-preparative HPLC (MeOH/H_2O, 11%, flow rate: 3 mL/min) to yield **1** (5.5 mg, R_t = 24 min) and **3** (3.2 mg, R_t = 23 min). Fr.2.1 (11 g) was separated by using a RP-18 column (MeOH/H_2O, 10%–70%) to generate three fractions (Fr.2.1.1–Fr.2.1.3). Of which, Fr.2.1.2 (3 g) was subjected to Sephadex LH-20 (MeOH) followed by semi-preparative HPLC (MeOH/H_2O, 20%, flow rate: 3 mL/min) to yield **2** (4.5 mg, R_t = 16 min).

4.4. Compound characterization data

4.4.1. Choushenoside A (1)

Brown yellow powder; $[\alpha]_D^{21.9}$–139.1 (*c* 0.24, MeOH); UV (MeOH) λmax (log*ε*) 286 (3.45), 229 (3.89), 208 (4.35) nm; CD (MeOH) Δ*ε*204 +74.10, Δ*ε*217 –79.09, Δ*ε*281 –3.80; ESIMS *m/z* 939 $[M+Na]^+$, HRESIMS *m/z* 939.2521 $[M+Na]^+$ (calcd for $C_{43}H_{48}NaO_{22}$, 939.2535); ^{1}H and ^{13}C NMR data, see Table 1.

4.4.2. Choushenoside B (2)

Brown yellow powder; $[\alpha]_D^{21.9}$ − 120.6 (*c* 0.23, MeOH); UV (MeOH) λmax (log*ε*) 289 (3.33), 231 (3.78), 207 (4.25) nm; CD (MeOH) Δ*ε*200 +19.43, Δ*ε*218 –43.85, Δ*ε*282 –1.85; ESIMS *m/z*939 $[M+Na]^+$, HRESIMS *m/z* 939.2525 $[M+Na]^+$ (calcd for $C_{43}H_{48}NaO_{22}$,939.2535); ^{1}H and ^{13}C NMR data, see Table 2.

Table 2
^{1}H (600 MHz) and^{13}C NMR (150 MHz) data of **2** in methanol-d_4 (*δ* in ppm, *J* in Hz).

Position	δ_H	δ_C	Position	δ_H	δ_C
2	4.77, d (7.3)	83.1 CH	2‴	4.44, d (7.9)	83.5 CH
3	4.07, m	68.1 CH	3‴	3.87, m	68.8 CH
4	2.85, dd (16.4, 5.2) 2.60, dd (16.4, 7.6)	28.2 CH_2	4‴	2.80, dd (16.3, 5.5) 2.41, dd (16.3, 8.6)	29.4 CH_2
5		155.1 C	5‴		155.6 C
6	6.29, s	96.1 CH	6‴		110.5 C
7		156.2 C	7‴		156.2 C
8		108.7 C	8‴	6.19, s	95.7 CH
9		153.6 C	9‴		154.5 C
10		103.2 C	10‴		104.3 C
1′		131.2 C	1⁗		132.0 C
2′	6.83, br. s	115.6 CH	2⁗	6.75, overlap	115.2 CH
3′		146.1 C	3⁗		146.3 C
4′		146.2 C	4⁗		146.4 C
5′	6.75, overlap	116.0 CH	5⁗	6.72, overlap	116.2 CH
6′	6.61, br. d (8.0)	120.0 CH	6⁗	6.72, overlap	120.1 CH
1″	4.79, d (7.8)	102.6 CH	1⁗′	4.78, d (7.8)	102.2 CH
2″	3.65, t (8.2)	74.5 CH	2⁗′	3.61, t (8.3)	74.7 CH
3″	3.43, overlap	78.0 CH	3⁗′	3.43, overlap	78.1 CH
4″	3.43, overlap	71.1 CH	4⁗′	3.43, overlap	71.2 CH
5″	3.43, overlap	77.9 CH	5⁗′	3.43, overlap	78.0 CH
6″	3.84, overlap; 3.74, m	62.2 CH_2	6⁗′	3.91, d (11.8); 3.74, m	62.4 CH_2
CH_2	4.03, d (15.1) 3.86, overlap	17.6 CH_2			

Table 3
^{1}H (600 MHz) and ^{13}C NMR (150 MHz) data of **3** in DMSO-d_6 (δ in ppm, J in Hz).

Position	δ_H	δ_C	Position	δ_H	δ_C
2	4.57, d (6.2)	80.5 CH	2‴	4.64, d (5.7)	78.5 CH
3	3.81, m	66.0 CH	3‴	3.90, m	64.2 CH
4	2.77, dd (16.4, 4.8)[a]	26.8 CH_2	4‴	2.77, dd (16.3, 4.8)[a]	26.1 CH_2
	2.65, dd (16.4, 6.4)[a]			2.42, dd (16.3, 7.2)[a]	
5		153.6 C	5‴		156.1 C
6	6.27, s	94.0 CH	6‴	6.05, d (1.6)	95.6 CH
7		154.9 C	7‴		156.6 C
8		108.0 C	8‴	5.91, br. s	94.5 CH
9		152.1 C	9‴		155.6 C
10		101.3 C	10‴		101.7 C
1′		129.1 C	1⁗		130.7 C
2′	6.62, br. s	113.9 CH	2⁗	6.59, s	113.2 CH
3′		144.6 C	3⁗		143.5 C
4′		144.7 C	4⁗		143.8 C
5′	6.64, d (8.4)	115.0 CH	5⁗	6.47, s	119.2 CH
6′	6.48, br. d (8.0)	117.7 CH	6⁗		125.0 C
1″	4.70, d (7.6)	98.8 CH	1⁗′	4.70, d (7.6)	100.5 CH
2″	2.97, t (8.2)	73.2 CH	2⁗′	3.16, overlap	73.0 CH
3″	3.23, overlap	76.8 CH	3⁗′	3.23, overlap	76.9 CH
4″	3.17, overlap	69.5 CH	4⁗′	3.17, overlap	69.4 CH
5″	3.23, overlap	76.5 CH	5⁗′	3.23, overlap	76.0 CH
6″	3.70, overlap	60.0 CH_2	6⁗′	3.70, overlap	60.4 CH_2
	3.53, m			3.53, m	
7-OH	9.37, s		5‴-OH	9.28, s	

[a] Recorded at 400 MHz in methanol-d_4.

4.4.3. Choushenoside C (3)

Brown yellow powder; $[\alpha]_D^{22.5}$–45.4(c 0.29, MeOH); UV (MeOH) λmax (logε) 285 (3.34), 208 (4.22) nm; CD (MeOH) $\Delta\varepsilon$203 +7.41, $\Delta\varepsilon$218 –18.60, $\Delta\varepsilon$279 –2.95; ESIMS m/z 925 $[M+Na]^+$, HRESIMS m/z 925.2379 $[M+Na]^+$ (calcd for $C_{42}H_{46}NaO_{22}$,925.2378); ^{1}H and ^{13}C NMR data, see Table 3.

4.5. Acid hydrolysis

Independent solutions of **1, 2** and **3** (1.0 mg) in 1 N HCl were stirred at 70 °C for 5 h. After cooling, the mixtures were extracted with EtOAc. In each case, the aqueous layer was neutralized with 1 N NaOH and concentrated in vacuo giving a residue that was dissolved in anhydrous pyridine (2 mL). To each of these solutions was added L-cysteine methyl ester hydrochloride (2 mg) and the resulting mixtures were stirred at 60 °C for 1 h and concentrated in vacuo at 0 °C. Slow addition of 1-(trimethylsiyl)imidazole to the mixtures was followed by stirring at 60 °C for 1 h. Aliquots (4 μL) of the supernatants were subjected to chiral GC analysis to demonstrate that D-glucose is present in **1, 2** and **3** (Shi et al., 2014).

4.6. SIRT1 inhibition

To test for SIRT1 inhibition, each well of a plate was created containing 0.5U of SIRT1 enzyme, 1000 μM of NAD+ (Enzo Life Sciences), 100 μM of SIRT1 peptide substrate (Enzo Life Sciences), and the SIRT1 assay buffer (50 mM Tris-HCl, pH 8.0, 137 mM NaCl, 2.7 mM KCl, 1 mM $MgCl_2$, 1 mg/mL BSA) along with the test compound at a specific concentration. The plate was incubated at 37 °C for 30 min and then subjected to Fluor de Lys developer solution (Enzo Life Sciences) containing 2 mM nicotinamide. The plate was incubated at 37 °C for another 30 min and the wells were read by using a fluorimeter with an excitation wavelength of 360 nm and emission wavelength of 460 nm (Karbasforooshana and Karimib, 2017).

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Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.phytochem.2018.05.012.

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