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An anti-inflammatory C-stiryl iridoid from *Camptosorus sibiricus* Rupr.

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ABSTRACT

A new iridoid glycoside, named camptoside (**1**), together with three known compounds as dehydrodiconiferyl alcohol-9′-*O*-*β*-D-glucopyranoside (**2**), aesculetin (**3**) and vajicoside (**4**), have been isolated from *Camptosorus sibiricus* Rupr. (Aspleniaceae). Their structures were established on the basis of spectroscopic analysis, especially 1D- and 2D-NMR data, and by comparison of their spectroscopic and physical data with those reported in the literature. Compounds **1–3** exhibited inhibitions of nitric oxide production in lipopolysaccharide-induced RAW 264.7 macrophages with IC_{50} values of 11.2, 8.3 and 9.4 μM, respectively.

1. Introduction

Thromboangiitis obliterans, also known as Buerger's disease, is an incurable disease characterized by recurring progressive inflammation and clotting in small and medium arteries and veins of the hands and feet [1]. In many cases, patients with the disease are treated with surgery, antiplatelet aggregation or dilatation drugs [2]. Although the etiology of Buerger's disease is still unknown [3], the feature of the inflammatory pathology of it suggests that alleviating inflammation during this ischemic condition occurrence could potentially be beneficial.

Camptosorus sibiricus Rupr., widely distributed in the North of China, is a famous folk medicine with good therapeutic effects on thromboangiitis obliterans, liver cancer and traumatism [4]. Previous chemical and pharmacological studies resulted in characterization of constituents with various structural features and biological activities. Up to now, > 50 organic compounds have been isolated from the whole herb of this plant, including flavonoids, triterpenoid saponins, organic acids, disaccharose, polyols and nitrogen containing entities [5–14].

Our previous screening showed that the total flavonoids of *C. sibiricus* could improve the condition of rats with Buerger's disease [15], however, the active constituents corresponding to this effect have not been identified clearly. The present research is aiming at finding compounds related to the action in *C. sibiricus,* and one new iridoid glycoside, camptoside (**1**), along with three known compounds, dehydrodiconiferyl alcohol-9′-*O*-*β*-D-glucopyranoside (**2**) [16], aesculetin (**3**) [17], and vajicoside (**4**) [18] were discovered (Fig. 1). Anti-inflammatory effects of them were tested *in vitro*.

2. Results and discussion

Compound **1** was obtained as a yellow gel with $[\alpha]_D^{20}$ + 50.5 (*c* 0.18, MeOH). The IR spectrum of **1** showed absorption band for hydroxyl (3340 cm^{-1}), carbonyl (1691 cm^{-1}), and aromatic (1611 and 1514 cm^{-1}) functional groups (Fig. S1). The positive mode ESIMS (Fig. S2) of **1** gave a quasi-molecular ion peak at *m/z* 524 $[M + NH_4]^+$. The molecular formula $C_{25}H_{30}O_{11}$ was indicated on the basis of high-resolution electrospray ionization mass spectroscopy (HRESIMS) at *m/z* 529.1658 $[M + Na]^+$ (calcd for $C_{25}H_{30}O_{11}Na$, 529.1680, Fig. S3), and NMR data (Table 1 and Fig. S4 to S10). The ^1H NMR spectrum (Fig. S4) of **1** in CD_3OD exhibited 24 proton signals characteristic of a *para*-substituted phenyl group at δ_H 7.21 (2H, d, J = 8.4 Hz) and 6.70 (2H, d, J = 8.4 Hz), a trans-double bond at δ_H 6.30 (1H, d, J = 15.6 Hz) and 6.12 (1H, dd, J = 15.6 and 7.8 Hz), two triply substituted double bonds at δ_H 7.47 (1H, d, J = 1.2 Hz) and 5.68 (1H, brs), two acetal proton at δ_H 5.45 (1H, d, J = 5.4 Hz, H-1) and 4.68 (d, J = 7.8 Hz, H-1′), a methoxyl group at δ_H 3.63 (3H, s), and other oxygenated-like oxymethines or oxymethylenes. The ^{13}C NMR and DEPT spectra (Fig. S5

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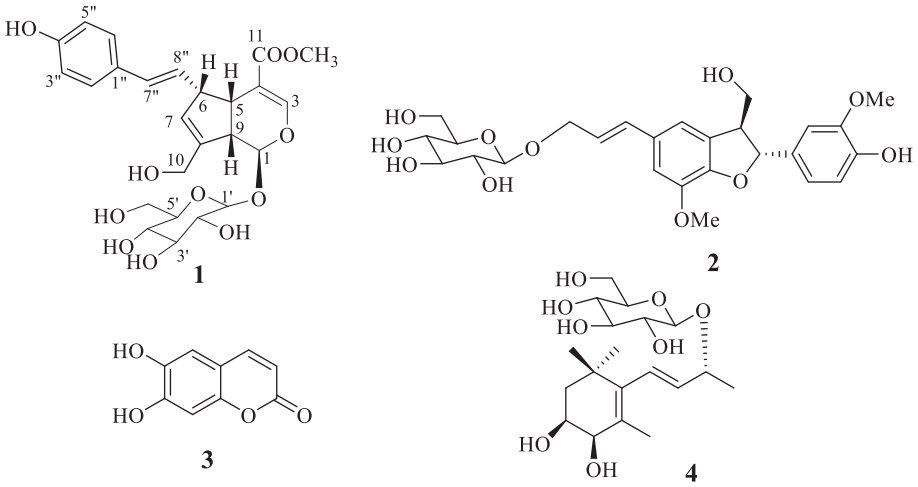

Fig. 1. Structures of isolated compounds from *C. sibiricus* Rupr.

Table 1
^{1}H and ^{13}C NMR spectral data (δ) for compounds **1**[a].

No.	δ_H	δ_C	^{1}H-^{1}H COSY selected	HMBC selected (from ^{1}H to ^{13}C)
1	5.45 d (5.4)	96.9	H-9	C-1′
3	7.47 d (1.2)	153.2	H-5(weak)	C-1,4,5,11
4	–	112.1	–	–
5	3.10 ddd (8.4, 6.0, 1.2)	42.4	H-6,9	C-4,9, 8″
6	3.21 dd (8.4, 7.8)	56.0	H-5,7, 8″	ND
7	5.68 brs	131.6	H-6, 9,10a,10b	C-5,6,8,9,10
8	–	144.7	–	–
9	2.98 dd (6.0, 5.4)	47.1	H-1,5	C-4,8
10a	4.32 brd (14.4)	61.0	H-6, 7, 10b	C-7,8
10b	4.21 brd (14.4)		H-10a	
11	–	169.6	–	–
OC*H*$_3$–11	3.63 s	51.7	–	C-11
1′	4.68 d (7.8)	100.2	H-2′	C-1
2′	3.20 [b] m	74.8	H-1′,3′	C-1′,3′,5′
3′	3.28 [b] m	78.4	H-2′,4′	C-4′
4′	3.27 [b] m	71.6	H-3′,5′	C–3′,5′,6′
5′	3.37 [b] m	77.9	H-4′,6'a,6'b	C-4′
6'a	3.88 dd (12.0,1.8)	62.7	H-5′,6'b	ND
6'b	3.66 dd (12.0,5.4)		H-5′,6'a	
1″	–	130.7	–	–
2″, 6″	7.21 d (8.4)	128.3	H-3″,5″	C-4″,7″
3″, 5″	6.70 d (8.4)	116.3	H-2″, 6″	C-1″, 4″
4″	–	157.8	–	–
7″	6.30 d (15.6)	130.3	H-8″	C-6, 2″, 6″
8″	6.12 dd (15.6,7.8)	130.1	H-6,7″	C-1″

[a] NMR data (δ) were measured in CD_3OD at 600 MHz for ^{1}H and 150 MHz for ^{13}C. Proton coupling constants (J) in Hz are given in parentheses.
[b] Signals in this region were overlapped. ND means the signal was not detected.

and S6) of **1** showed the presence of all 25 carbons, including one methyl carbon signal at δ_C 51.7 ppm; two methylene carbon signals at δ_C 61.0 and 62.7 ppm, respectively; seventeen methine carbon and five quaternary carbon signals [one of them was oxygen-bearing aromatic carbon at δ_C 157.8 (C-4″)] and one carbonyl carbon [δ_C 169.6 (C-11)]. All these signals above suggested that **1** should be an iridoid glycoside analogue [19–21]. The ^{1}H signals at δ_H 4.68 (d, J = 7.8 Hz, H-1′), 3.88 (dd, J = 10.2 and 1.8 Hz, H-6'a) and 3.66 (dd, J = 10.2 and 5.4 Hz, H-6'b) together with the ^{13}C signals (C1′-C6′ in Table 1) assigned to the sugar unit proved that it was a β-glucopyranosyl unit [22]. This suggestion was confirmed by enzymatic hydrolysis of **1**: the glucose was detected by thin layer chromatography (TLC) analysis of the hydrolysate and was isolated by HPLC. The same optical rotation values between this glucose $[\alpha]_D^{20}$ + 43.1 (c 0.12, H_2O)] and that of β-D-glucose [22] indicated that the saccharide unit in **1** was indeed a β-glucopyranosyl unit.

Comparing the ^{1}H and ^{13}C NMR data of **1** to those of compound *E*-6-*O*-*p*-coumaroyl scandoside methyl ester in the literature [21 (^{1}H NMR); 19 (^{13}C NMR)], as well as those we acquired in the same solvent (Fig. S12 and S13, and Table S1), indicated that **1** was very similar with *E*-6-*O*-*p*-coumaroyl scandoside methyl ester, except for the different signals corresponding to a *E*-4-hydroxystyryl group in **1** instead of a *O*-4-hydroxycinnamic acyl ester group in *E*-6-*O*-*p*-coumaroyl scandoside methyl ester (Fig. 1). This was supported by the different chemical shifts of H-7″ (6.30 ppm in **1** and 7.63 ppm in the later one), C-7″ (130.3 ppm in **1** and 144.9 ppm in the later one), and as well as other related signals around the *E*- 4-hydroxystyryl. What's more, the molecular weight of **1**, showing 44 Da lower than that of *E*-6-*O*-*p*-coumaroyl scandoside methyl ester, also confirmed this difference.

Further analysis of the NMR data of **1** led us to found significantly upfielded chemical shifts of H-6 [$\Delta\delta_H$ -2.20 ppm] and C-6 [$\Delta\delta_C$ -26.0 ppm]. Therefore, the additional styryl unit should be connected to C-6. The structure of **1** was confirmed by 2D NMR data analysis. The proton and corresponding carbon resonances in the 2D NMR spectra of **1** were assigned by the gradient heteronuclear single quantum coherence (gHSQC, Fig. S7) experiment. The HMBC (Fig. S8) correlations from H-7″ to C-2″ and C-6″, together with their shifts, proved the presence of 4-hydroxylstyryl moiety. Although the key HMBC correlations of H-6/C-7″ and H-8″/C-5 and C-7 were absent in the spectrum for the minor quantity of sample, the ^{1}H−^{1}H gCOSY (Fig. S9 and S11) correlations of H-7/H-6/H-8″/H-7″ together with the HMBC correlations of H-7″with C-6, confirmed that the 4-hydroxylstyryl moiety was located at C-6. Therefore, the planar structure of **1** was elucidated as an iridoid glycoside possessing a hydroxylstyryl unit substituted at C-6.

Given the key correlations of NOESY (Fig. S10) were absent, the relative configuration of C-6, C-5 and C-9 in **1** were determined on the basis of vicinal coupling constants. H-5 in **1** showed a *ddd* peak shape with coupling constants of 8.4 ($J_{H\text{-}5/H\text{-}6}$), 6.0 ($J_{H\text{-}5/H\text{-}9}$), and 1.2 ($J_{H\text{-}5/H\text{-}3}$) Hz, respectively (Fig. S4), indicated that the orientation of H-5 and H-6 were at same sides of the plane, which was different from that in *E*-6-*O*-*p*-coumaroyl scandoside methyl ester (Table S1). Meanwhile, H-6 should be oriented on the opposite direction in **1** to that in *E*-6-*O*-*p*-coumaroyl scandoside methyl ester. For the coupling constant of H-5/H-9 was 6.0 Hz, very similar to that in the *E*-6-*O*-*p*-coumaroyl scandoside methyl ester (6.6 Hz of $J_{H\text{-}5/H\text{-}9}$ in the literature), therefore, H-5 and H-9 should have the same orientation as that in *E*-6-*O*-*p*-coumaroyl

scandoside methyl ester. The double split peaks of H-1 in ^{1}H NMR spectrum, with a coupling constant of 5.4 Hz between H-1 and H-9, suggested that H-1 was oriented at the opposite side to H-9, and the same to that in *E*-6-*O*-*p*-coumaroyl scandoside methyl ester. Further investigation of the literature, led us to find that compound **1** showed the same configuration of C-6, C-5 and C-9 with that of 10-cafeyl deacetyl daphylioside [23] and 10-*O*-dehydroferuloyl-10-*O*-deacetyl daphylioside [24]. Especially, the similar coupling constant of $J_{5,6}$ (8.4 Hz in **1** and 8.0 Hz in other two) was also confirmed the Cis orientation of H-5 and H-6 in **1**. Based on the above evidence, the structure of **1** was established as shown in Fig. 1, and was named camptoside.

Compound **1** was determined as a novel iridoid glycoside with an *E*-4-hydroxystyryl group connected to C-6 position by a carbon-carbon bond. For some amount of *E*-6-*O*-*p*-coumaroyl scandoside methyl ester was isolated in our recently re-investigated of *Camptosorus sibiricus* Rupr. (Aspleniaceae), compound **1** was seemed to be a product through a rearrangement reaction with de-carbon-dioxide of *E*-6-*O*-*p*-coumaroyl scandoside methyl ester, due to this kind of reaction was commonly occurred in the fragmentation pattern in MS. A similar reaction was designed and conducted by heating the *E*-6-*O*-*p*-coumaroyl scandoside methyl ester DMSO solution (2.0 mg/mL, 60 °C) for two hours, however, there not any amount of **1** was detected in the reaction mixture by HPLC.

The structure of the novel compound **1** differs from the one of iridoid esters by formal extrusion of carbon dioxide and coupling between the resulting alkyl(alkenyl) residues. No example of this reaction seems to have been reported in biological systems, and an alternative could be the trapping of a iridoid cation by a nucleophilic C6-C2 acetylenic compound.

Compounds **1–4** were examined for anti-inflammatory activity by evaluating the inhibition of lipopolysaccharide (LPS) induced NO production in RAW 264.7 macrophages. As shown in Table 2, compounds **1–3** showed strong potencies in inhibiting NO production and had no influence on cell viability.

3. Experimental

3.1. General experimental procedures

Optical rotations were measured on P-2000 polarimeter (JASCO, Tokyo, Japan). UV spectra were measured on a UV-2550PC spectrometer (SHIMADZU). IR spectra were recorded on a Nicolet iN 10 Micro FTIR spectrometer. NMR spectra were obtained at 400 or 600 MHz for ^{1}H, and 100 or 150 MHz for ^{13}C, respectively, on a Bruker Avance AVIII-600 or 400 MHz spectrometer with solvent peaks used as references. ESIMS and HRESIMS data were measured using an LTQ Orbitrap XL instrument. Column chromatography (CC) was performed with silica gel (200–300 mesh, Qingdao Marine Chemical Inc. Qingdao, China) and Sephadex LH-20 (Pharmacia Biotech AB, Uppsala, Sweden). HPLC separation was performed on an instrument consisting of a Waters 600 controller, a Waters 600 pump, and a Waters 2487 dual λ absorbance detector (Waters Corporation, Milford, USA), with a YMC-Pack ODS-A (250 × 10 mm i.d.) column packed with C_{18} (5 μm) (YMC Co., Ltd., JAPAN). TLC was carried out with glass precoated silica gel GF_{254} plates (Qingdao Marine Chemical Inc.). Spots were visualized under UV light or by spraying with 7% H_2SO_4 in 95% EtOH followed by heating. Unless otherwise noted, all chemicals were obtained from commercially available sources and were used without further purification.

Table 2
Inhibitory effects of compounds **1–4** against LPS induced NO production in RAW 264.7 macrophage cells.

Compounds	IC_{50} (μM)[a]	cell viability (%)[b]
1	11.2	87.5 ± 3.7
2	8.3	92.5 ± 2.1
3	9.4	90.1 ± 3.4
Curcumin[c]	10.1	83.4 ± 2.5

[a] The IC_{50} value of each compound was defined as the concentration (μM) that caused 50% inhibition of NO production in LPS-activated RAW 264.7 macrophage cells. Compounds **4** were inactive (IC_{50} > 50 μM).

[b] Cell viability was expressed as a percentage (%) of the LPS-only treatment group.

[c] Positive control. The results are averages of three independent experiments, and the data are expressed as means ± SD.

3.2. Plant material

The *Camptosorus sibiricus* Rupr. were collected in April 2017 from Yuzhou city, Henan Province of People's Republic of China. Plant identity was verified by professor Qi Guo of the Shandong Academy of Pharmaceutical Sciences, where a voucher specimen (No. 20160425) is deposited.

3.3. Extraction and isolation

The air-dried whole herbs of *C. sibiricus* Rupr. (17.4 kg) were extracted with 11.0 L of 95% EtOH at room temperature for 3 × 48 h. The ethanol extract was evaporated under reduced pressure to yield a dark brown residue (528.6 g), which was suspended in H_2O (1.5 L) and partitioned with EtOAc (6 × 1 L). The aqueous phase was applied to a AB-8 macroporous adsorbent resin (1000 g) column. Successive elution of the column with H_2O, 30% EtOH, 50% EtOH, and 95% EtOH (5000 mL each) yielded four corresponding fractions after removing solvents. The fraction eluted by 50% EtOH (97 g) was chromatographed over silica gel, eluting with increasing amounts of methanol (0–100%) in dichloromethane, to afford ten fractions (A–E) based on TLC analysis. Fraction B (22 g) was chromatographed over Sephadex LH-20 eluting with dichloromethane/methanol (1:1) to yield B-1–B-4. B-3 (4.3 g) was separated *via* RP-MPLC eluting with a gradient of MeOH (5–100%) in H_2O to give B-3-1–B-3-6. Separation of B-3-3 (621 mg) by a normal-phase silica gel column (EtOAc/95%EtOH, 30:1) yielded B-3-3-1–B-3-3-5. B-3-3-2 (126 mg) was separated by RP flash CC (10–90% MeOH in H_2O) to afford B-3-3-2-1-B-3-3-2-6, and purification of B-3-3-2-4 (23 mg) by RP HPLC (38% MeOH in H_2O) gave **3** (4.5 mg) and **4** (11.5 mg). Fractions B-3-3-4 (58 mg) was isolated by preparative TLC (mobile phase: EtOAc/95%EtOH, 15:1), followed by RP HPLC separation (42% MeOH in H_2O) to yield **2** (3.3 mg). Fraction B-3-5 (103 mg) was isolated by preparative TLC (mobile phase: EtOAc/95%EtOH/CH_3COOH, 15:1:1), followed by RP HPLC separation (25% MeCN in H_2O) to yield **1** (22.4 mg).

3.3.1. Camptoside (1)

Yellow gel; $[\alpha]_D^{20}$ + 50.5 (*c* 0.18, MeOH); IR (KBr) ν_{max} 3340, 2920, 1691, 1629, 1611, 1514, 1440, 1376, 1288, 1160, 1077, 1047, 888, 841, 806, 768 cm^{-1}; ^{1}H NMR (CD_3OD, 600 MHz) and ^{13}C NMR (CD_3OD, 150 MHz) spectral data, see Table 1; (+)-ESIMS *m/z* 524 $[M + NH_4]^+$; (+)-HRESIMS *m/z* 529.1658 $[M + Na]^+$ (calcd for $C_{25}H_{30}O_{11}Na$, 529.1680).

3.3.2. Enzymatic hydrolysis of 1

A solution of compound **1** (10 mg) in H_2O (3 mL) was treated with β-glucosidase from almonds (Fluka) (10 mg) at 37 °C for 30 h. The reaction mixtures were extracted with EtOAc (3 × 3 mL). The H_2O phases of the hydrolyzate was concentrated to dryness, and chromatographed on a silica gel column, eluting with CH_3CN-H_2O (8:1), to yield glucose with $[\alpha]_D^{20}$ + 43.1 (*c* 0.12, H_2O). The solvent system $CHCl_3$-MeOH-H_2O (8:5:1) was used for TLC identification of glucose (Rf, 0.32).

3.3.3. Anti-inflammatory bioassay

The experiment was performed as previously described [25], and

using curcumin as positive control. Briefly, RAW 264.7 macrophages were harvested and seeded in 96-well plates (1×10^4 cells/well) for measurement of NO production. The plates were treated with LPS (1.0 *μg/mL*) in the presence or absence of test compounds for 24 h. The amount of NO was determined by the nitrite concentration in the cultured RAW 264.7 macrophage supernatants using the Griess reagent. In order to investigate whether the inhibitory activities were due to the decrease of cell number (cytotoxicity), the effects of the compound on cell viability were measured using the MTT method.

4. Conclusions

In this study, a new compound **1**, along with three known compounds (**2–4**) were isolated from an EtOH (95%) extract of the whole herbs of *Camptosorus sibiricus* Rupr. (Aspleniaceae). Compounds (**1–3**) exhibited the same inhibitory activity against NO production as the positive control. Therefore, these compounds should be the potential active components that contributed to the Buerger's disease in this herb.

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Conflict of interest

The authors declare that they have no conflict of interest.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.fitote.2019.03.009.

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