Schistosomicidal and Antioxidant Flavonoids from *Astragalus englerianus*

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Key words
- *Astragalus englerianus*
- Fabaceae
- flavonoids
- schistosomicidal
- antioxidant activity

Abstract

Astragalus englerianus is a close relative of the traditional Chinese medicine plant Radix Astragali (Huang-qi) and is mainly distributed in Yunnan. It has been traditionally used as a substitute of "Huang-qi" for reducing fatigue and enhancing immunity by local folks. A phytochemical study of the methanol extract of the roots led to the isolation of three new flavonoids including one aurone (**1**) and two chalcones (**2** and **3**), as well as two known flavonoids (**4** and **5**). Their structures were elucidated based on the analyses of extensive spectroscopic data and comparison of their physicochemical properties. This is the first report on the occurrence of *β*-hydroxydihydrochalcone, 2′,5′-dioxygenchalcones, and 2′,5′-dioxygenaurone in the genus *Astragalus*. All the isolated compounds were tested *in vitro* for their schistosomicidal and antioxidant activities. Compounds **2** and **4** showed schistosomicidal activities with worm mortality rates of 100% within 12 h in a drug-containing (0.70 and 0.77 mM, respectively) RPMI 1640 medium. Compounds **1** and **2** exhibited antioxidant activities in 2,2-diphenyl-1-(2,4,6-trinitrophenyl)hydrazyl free radical scavenging assays, with IC_{50} values of 35.9 ± 1.1 and 12.2 ± 1.1 μM, respectively.

Supporting information available online at http://www.thieme-connect.de/products

Introduction

As an important traditional Chinese medicine, Radix Astragali (Huang-qi) has been used for more than two thousand years to enhance and regulate immune function and to promote metabolism. It has been verified to possess antifatigue, anti-anoxia, anti-radiation, and hepatoprotective activities [1,2]. Official materials used as Radix Astragali come from two *Astragalus* plants, *Astragalus membranaceus* and *Astragalus membranaceus* var. *mongholicus*. However, neither of these grow in Yunnan [3]. *Astragalus* plants distributed in China include 278 species, two subspecies, 35 varieties, and two forms [4]. Among them, at least 51 *Astragalus* species can be found in Yunnan, and most of them are used as substitutes for "Huang-qi" by local folks and display similar medicinal effects to Radix Astragali [1]. Although *Astragalus* resources in Yunnan are exceptionally rich, most *Astragalus* plants have not been systematically studied yet. Unfortunately, due to environmental changes and human influences, some *Astragalus* plants in Yunnan became endangered during the past several decades. It is, therefore, necessary to perform urgent studies on *Astragalus* plants for both scientific research and plant preservation purposes. In this study, one Yunnan native and commonly used *Astragalus* plant, *Astragalus englerianus* Ulbr. (Fabaceae or Leguminosae), was selected for chemical and bioactive studies. This paper is the first report of natural products from *A. englerianus*.

Results and Discussion

Three new flavonoids, (*Z*)-2′,5′-dihydroxy-6-methoxyaurone (**1**), 2,2′,5′-trihydroxy-4-methoxychalcone (**2**), and (*βR*)-2,2′,5′,*β*-tetrahydroxy-4-methoxydihydrochalcone (**3**), together with two known flavonoids, (3*R*)-sativan (**4**) [5,6] and (6a*R*,11a*R*)-maackiain (**5**) [7], were isolated and identified from the methanol extract of the root (**Fig. 1**).

Compound **1** was assigned the molecular formula $C_{16}H_{12}O_5$ (11 unsaturation degrees) from its HR-EI-MS. The IR spectrum showed absorption

received May 10, 2014
revised July 25, 2014
accepted October 5, 2014

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DOI http://dx.doi.org/10.1055/s-0034-1383219
Published online November 5, 2014
Planta Med 2014; 80: 1727–1731 © Georg Thieme Verlag KG Stuttgart · New York · ISSN 0032-0943

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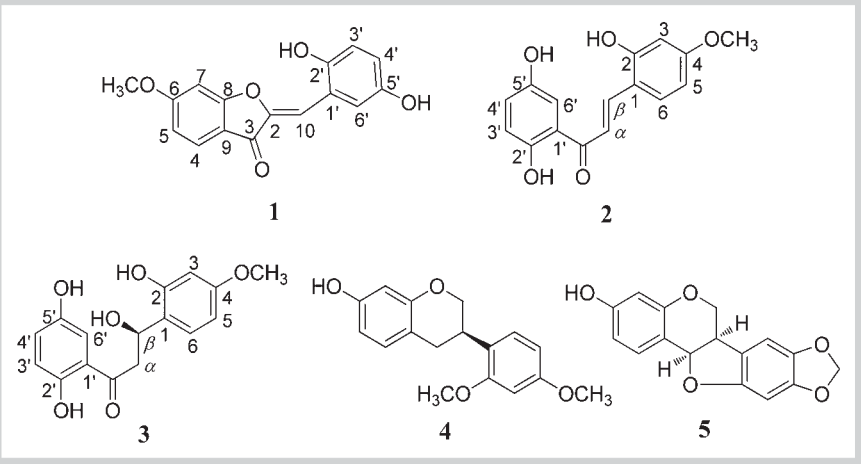

Fig. 1 Structures of compounds **1**–**5**.

Table 1 NMR spectroscopic data of compounds **1**–**3**.

Position	1[a]		2[b]		3[c]	
	δ_H (multi, *J* in Hz)	δ_C	δ_H (multi, *J* in Hz)	δ_C	δ_H (multi, *J* in Hz)	δ_C
1				116.1		119.6
2		148.4		160.0		156.6
3		183.1	6.57 (d, 2.3)	102.3	6.42 (d, 2.5)	102.2
4	7.76 (d, 8.3)	126.1		164.4		162.2
5	6.75 (brd, 8.3)	113.1	6.53 (dd, 8.6, 2.3)	107.7	6.49 (dd, 8.56, 2.5)	106.0
6		167.9	7.75 (d, 8.6)	132.1	7.40 (d, 8.56)	128.8
7 (-CO-)	6.53 (brs)	97.3		194.8		195.5
8 (α)		168.9	7.84 (d, 15.4)	118.3	3.02 (dd, 17.0, 13.5) 2.79 (dd, 17.0, 2.7)	44.5
9 (β)		115.9	8.26 (d, 15.4)	142.2	5.65 (dd, 13.5, 2.7)	76.3
10	8.13 (s)	107.7				
1′		121.6		121.0		122.2
2′		152.4		157.8		157.5
3′	7.20 (overlap)	117.9	6.86 (d, 8.9)	119.5	6.94 (d, 8.9)	120.2
4′	7.24 (overlap)	120.8	7.13 (dd, 8.9, 2.9)	125.4	7.05 (dd, 8.9, 3.1)	125.9
5′		152.8		150.1		152.9
6′	8.42 (brs)	118.4	7.56 (d, 2.9)	115.4	7.23 (d, 3.1)	111.4
-OCH_3	3.75 (s)	56.7	3.80 (s)	55.8	3.77 (s)	55.7
2′-OH			12.64 (s)			
-OH			9.48 (brs)			

[a] Recorded at 400 MHz for ^{1}H NMR and 100 MHz for ^{13}C NMR in pyridine-d_5; [b] Recorded at 400 MHz for ^{1}H NMR and 100 MHz for ^{13}C NMR in acetone-d_6; [c] Recorded at 400 MHz for ^{1}H NMR and 100 MHz for ^{13}C NMR in methanol-d_4

bands for hydroxyl (3405 cm^{-1}), conjugated carbonyl (1666 cm^{-1}), conjugated double bond (3025, 1629 and 910 cm^{-1}), and aromatic ring (3074, 1590, and 1501 cm^{-1}) functional groups. The ^{1}H NMR spectrum of **1** showed an ABX coupling system with protons at δ_H 7.76 (1H, d, *J* = 8.3 Hz, H-4), 6.75 (1H, brd, *J* = 8.3 Hz, H-5), and 6.53 (1H, brs, H-7), and one unknown coupling system with signals at δ_H 8.42 (1H, brs, H-6′), 7.24 (1H, overlap, H-4′), and 7.20 (1H, overlap, H-3′). The ^{1}H NMR spectrum of **1** also exhibited one trisubstituted ethylene structural unit at δ_H 8.13 (1H, s, H-10) and one methoxyl at δ_H 3.75 (3H, s). Analysis of the ^{13}C NMR spectrum with the aid of the DEPT spectra revealed the existence of 16 carbons (**Table 1**). The spectroscopic data mentioned above indicated that compound **1** should be an aurone. Comparison of the spectroscopic data with those of aurones previously reported [8–10] suggested that compound **1** was an aurone with three oxygen-containing substituents.

The structure of **1** was determined by 2D-NMR analyses. The correlations from the ^{1}H-^{1}H COSY spectrum suggested two segments (**Fig. 2**, bold). The HMBC correlations of methoxyl (δ_H 3.75, s) to C-6 (δ_C 167.9), of H-4 (δ_H 7.76, d, *J* = 8.3 Hz) to C-3 (δ_C 183.1), and of H-10 (δ_H 8.13, s) to C-3 and C-6′ (δ_C 118.4), as well as the other correlations shown in **Fig. 2**, confirmed that compound **1** was an aurone with three oxygen-bearing substituents at C-6, 2′ and 5′. Thus, compound **1** was identified as (*Z*)-2′,5′-dihydroxy-6-methoxyaurone.

Compound **2** possessed the molecular formula $C_{16}H_{14}O_5$ (10 double bond equivalents) according to HR-EI-MS. The IR spectrum showed absorption bands for hydroxyl (3395 and 3387 cm^{-1}), conjugated carbonyl (1639 cm^{-1}), conjugated *trans*-double bond (3020, 1611 and 987 cm^{-1}), and aromatic ring (3059, 1588 and 1511 cm^{-1}) functional groups. The ^{1}H NMR spectrum of **2** showed the signals of one methoxyl, two hydroxyls, two ABX coupling system hydrogens, and one double bond (**Table 1**), which con-

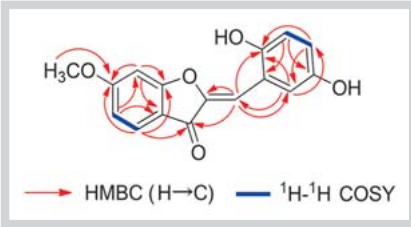

Fig. 2 Key ^{1}H-^{1}H COSY and HMBC correlations of compound **1**. (Color figure available online only.)

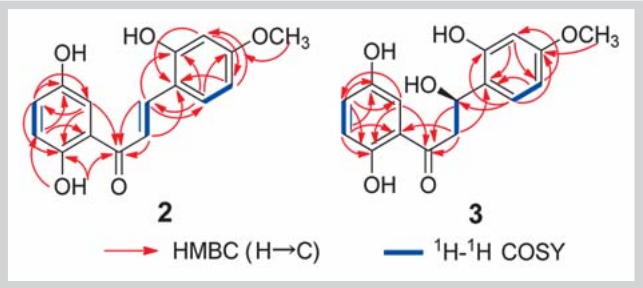

Fig. 3 Key ^{1}H-^{1}H COSY and HMBC correlations of compounds **2** and **3**. (Color figure available online only.)

firmed the existence of a conjugated *trans*-double bond in **2**. ^{13}C NMR and DEPT spectra displayed the existence of 16 carbons (**Table 1**) including one methoxyl, one carbonyl, and 14 olefinic carbons (including eight sp^2 methines, and six sp^2 quaternary carbons). After comparison of the spectroscopic data with those of known chalcones [8, 11], compound **2** was considered as a typical chalcone with four oxygen-containing substituents.

The correlations observed in the ^{1}H-^{1}H COSY spectrum suggested three fragments, H-5/H-6, H-3′/H-4′, and H-α/H-β (**Fig. 3**), which showed **2** having two ABX aromatic coupling systems. The ^{1}H NMR spectrum of **2** showed a hydrogen-bonded hydroxyl proton at δ_H 12.64 (1H, s) that can be assigned to the 2′-OH group, which was further confirmed on the basis of the correlations between 2′-OH and C-2′ (δ_C 157.8), C-3′ (δ_C 119.5), and carbonyl (δ_C 194.8) in the HMBC spectrum. A correlation of methoxyl (δ_H 3.80, s) to C-4 (δ_C 164.4) in the HMBC spectrum indicated that the methoxyl was at the position of C-4. Correlations of H-6′ (δ_H 7.56, d, J = 2.9 Hz) to C-2′ (δ_C 157.8), C-4′ (δ_C 125.4), and carbonyl (δ_C 194.8), of H-α (δ_H 7.84, d, J = 15.4 Hz) to C-1 (δ_C 116.1) and carbonyl (δ_C 194.8), and of H-β (δ_H 8.26, d, J = 15.4 Hz) to C-2 (δ_C 160.0), C-6 (δ_C 132.1), and carbonyl (δ_C 194.8) in the HMBC spectrum, as well as the other correlations depicted in **Fig. 3**, confirmed the chalcone skeleton and suggested that the other two hydroxyl groups were at C-2 and C-5′, respectively. Thus, compound **2** was proposed as 2,2′,5′-trihydroxy-4-methoxychalcone.

Compound **3** had the molecular formula $C_{16}H_{16}O_6$ (nine unsaturation degrees) on the basis of its HR-EI-MS. The IR spectrum showed absorption bands for hydroxyl (3405 and 3283 cm^{-1}), conjugated carbonyl (1671 cm^{-1}), and aromatic ring (3025, 1611, and 1513 cm^{-1}) functional groups. ^{1}H NMR and ^{13}C NMR spectral data of **3** (**Table 1**) were similar to those of **2** except for the disappearance of a disubstituted ethylene structural unit and the observation of an oxygen-bearing methine carbon at δ_C 76.3 and a methylene at δ_C 44.5. Further analyses of 2D NMR spectroscopic data (^{1}H-^{1}H COSY and HMBC, **Fig. 3**), and the specific rotation data $[\alpha]_D^{16.6}$ −18.82 (*c* 0.13, MeOH) of compound **3** and comparison with those of elatadihydrochalcone [12] allowed the spatial structure to be established. Therefore, compound **3** was deduced as (*βR*)-2,2′,5′,*β*-tetrahydroxy-4-methoxydihydrochalcone.

The two known compounds were identified as (3*R*)-sativan (**4**) [5, 6] and (6a*R*,11a*R*)-maackiain (**5**) [7] by comparison of their spectroscopic data and physicochemical properties with those reported in the literature.

Compounds **1**–**3** belonged to two types of flavonoids, and 2′,5′-dioxygenaurone, 2′,5′-dioxygenchalcone, and *β*-hydroxydihydrochalcone are all reported here for the first time in the genus *Astragalus*. In fact, they constitute a small subclass of flavonoids found in nature with only a few reports at all. Our findings may be useful for the chemical taxonomy. Since various bioactivities of flavonoids were reported recently, including antioxidant and antiparasitic activities [12–15], the schistosomicidal and antioxidant activities of all separated constituents were tested, and compounds **2** and **4** showed schistosomicidal activities, while **1** and **2** exhibited antioxidant activities.

All of the isolated compounds (**1**–**5**) were screened for their *in vitro* schistosomicidal and antioxidant activities. Compounds **2** and **4** caused worm mortality rates of 100% within 12 h in a drug-containing (0.70 and 0.77 mM, respectively) RPMI 1640 medium, and the other results are listed in **Table 2**. Compounds **1** and **2** exhibited stronger antioxidant activities than that of the positive control vitamin C (Vc, IC_{50} = 48.9 ± 1.1 μM), with IC_{50} values of 35.9 ± 1.1 and 12.2 ± 1.1 μM, respectively. Compound **3** showed a weak capability (IC_{50} = 871.7 ± 25.6 μM) of DPPH radical scavenging, and compounds **4** and **5** were inactive.

Materials and Methods

General

NMR spectra (1D and 2D NMR) were recorded on a Bruker Avance III-400 instrument with TMS as an internal reference. EI-MS and HR-EI-MS data were obtained on a Waters AutoSpec Premier P776 mass spectrometer. IR spectra were recorded by a Bruker Tensor 27 FT-IR spectrophotometer with KBr pellets. Optical rotations were determined on a Jasco P-1020 digital polarimeter, while UV data were obtained on a Shimadzu UV2401PC UV/Vis spectrophotometer. Optical density (OD) values in the antioxidant activity assay were analyzed on a BioTek Synergy HT microplate reader. Silica gel, RP-18, and Sephadex LH-20 were used for open column chromatography. Silica gel GF_{254} plates were used for TLC analyses. *Schistosoma japonicum* worms from rabbit hosts were provided by Prof. Yi-Mei Yang's Research Group (School of Basic Medicine, Dali University, China). Gibco RPMI 1640 medium and praziquantel (purity ≥ 98.0%) were used on the schistosomicidal activity experiments. 2,2-Diphenyl-1-(2,4,6-trinitrophenyl)hydrazyl (DPPH; purity ≥ 99.0%) and Vc (purity ≥ 98.0%) were used for the antioxidant activity assay.

Plant material

Roots of *A. englerianus* were collected in November 2011 from Cangshan Mountain, Dali, Yunnan Province, P.R. China. The plant material was identified by Dr. Chun-Lei Xiang (Kunming Institute of Botany, Chinese Academy of Sciences). A voucher specimen (No. 20100928–1b) has been deposited at the premises of Prof. Bei Jiang's Research Group, Institute of Materia Medica, Dali University.

Table 2 *In vitro* effects of compounds **1**–**5** against adult *S. japonicum*.

Group and concentration (mM)		Period of incubation in drug-containing medium							
		12 h		24 h		36 h		48 h	
		MR[a] (%)	VR[b] (%)	MR[a] (%)	VR[b] (%)	MR[a] (%)	VR[b] (%)	MR[a] (%)	VR[b] (%)
2.5%	**DMSO**	0	0	0	0	0	0	0	0
PZQ	0.12	100	100	66.7	91.7	50.0	87.5	33.3	83.3
1	0.70	0	50	0	66.7	0	70.8	66.7	87.5
	0.14	0	0	0	0	0	25	0	25
2	0.70	100	100	100	100	100	100	100	100
	0.14	0	50	0	50	0	50	0	50
3	0.66	0	25	0	25	66.7	91.7	100	100
	0.13	0	0	0	0	0	0	0	75
4	0.77	100	100	100	100	100	100	100	100
	0.15	0	0	0	25	0	25	0	25
5	0.70	0	0	0	75	100	100	100	100
	0.14	0	0	0	0	0	25	0	25

[a] MR: worm mortality rate; [b] VR: worm vigor reduction rate

Extraction and isolation

The air-dried roots (6.1 kg) were milled and extracted six times with methanol (6 × 25 L) at room temperature. After the extract solutions were combined and concentrated under reduced pressure, the resulting residue (480 g) was suspended in water and partitioned with ethyl acetate and *n*-BuOH successively. The ethyl acetate soluble portion (100 g) was adsorbed onto 100 g of silica gel (80–100 mesh) and chromatographed on a silica gel (1.2 kg, 200–300 mesh) column (diameter × height: 8.5 × 50 cm) eluted with a gradient of $CHCl_3$-CH_3COCH_3 (1 : 0 to 0 : 1, 80 L) to yield ten fractions (Frs. A–J). Fr. B (9.4 g) was purified by silica gel column chromatography (CC, 200–300 mesh, 3.2 × 30 cm) with petroleum ether (PE)-acetone (30 : 1 to 0 : 1, 10 L) to yield ten fractions (B_1–B_{10}). B_5 (1.6 g) was subjected to repeated CC over silica gel (300–400 mesh, 2.2 × 28 cm) with PE-EtOAc (8 : 1, 1.5 L) and $CHCl_3$-MeOH (240 : 1, 1 L), then was further purified by Sephadex LH-20 ($CHCl_3$-MeOH, 1 : 1, 0.3 L) and RP-18 CC (1.5 × 12 cm, MeOH-H_2O, 60% to 100%, 0.5 L) to afford compounds **4** (102.1 mg) and **5** (853.4 mg). Fr. C (5.7 g) was isolated by silica gel CC (200–300 mesh, 3.2 × 25 cm) with PE-acetone (10 : 1 to 0 : 1, 7 L) to yield eight fractions (C_1–C_8). C_5 (0.8 g) was successively subjected to silica gel CC (300–400 mesh, 1.5 × 28 cm) using $CHCl_3$-MeOH (240 : 1, 0.9 L) as the eluent, Sephadex LH-20 (MeOH, 0.3 L), and repeated silica gel CC (PE-EtOAc, 3 : 1, 0.5 L and $CHCl_3$-MeOH, 30 : 1, 0.4 L) to yield compounds **2** (98.0 mg) and **3** (67.2 mg). Fr. D (2.4 g) was purified by silica gel CC (300–400 mesh, 2.2 × 30 cm) with PE-EtOAc (3 : 1, 3 L) to yield six fractions (D_1–D_6). D_4 emerged as an orange red sediment after settling for several hours at room temperature, then was repeatedly washed with PE-EtOAc (3 : 1, 50 mL) to yield compound **1** (37.1 mg). All purified compounds had a degree of purity > 96% based on the TLC analyzed (all compounds exhibited one spot both under UV radiation and when sprayed with 8% H_2SO_4 in methanol) and NMR spectra (the baseline was smooth with trivial impurity peaks).

(Z)-2′,5′-Dihydroxy-6-methoxyaurone (**1**): orange red needle crystals (pyridine). UV (MeOH) λ_{max} (log ε): 254 (4.02), 288 (3.94), 334 (4.36), 415 (3.96) nm; IR (KBr) ν_{max}: 3405, 3382, 3074, 3025, 2834, 1666, 1629, 1590, 1573, 1501, 1433, 1300, 1273, 1025, 910, 869, 821, 811 cm^{-1}; EI-MS *m/z* (%): 284 $[M]^+$ (94), 267 (20), 151 (75), 84 (100); HR-EI-MS *m/z*: 284.0674 $[M]^+$ (calcd. for $C_{16}H_{12}O_5$, 284.0685); ^1H NMR (400 MHz, C_5D_5N) and ^{13}C NMR (100 MHz, C_5D_5N) data in ◉ **Table 1**.

2,2′,5′-Trihydroxy-4-methoxychalcone (**2**): red amorphous powder. UV (MeOH) λ_{max} (log ε): 259 (4.12), 384 (4.35) nm; IR (KBr) ν_{max}: 3395, 3387, 3059, 3026, 3020, 2842, 1639, 1611, 1588, 1511, 1486, 1441, 1301, 1235, 1201, 1021, 987, 846, 838, 824 cm^{-1}; EI-MS *m/z* (%): 286 $[M]^+$ (25), 256 (18), 255 (13), 150 (21), 137 (31); HR-EI-MS *m/z*: 286.0849 $[M]^+$ (calcd. for $C_{16}H_{14}O_5$, 286.0841); ^1H NMR (400 MHz, CD_3COCD_3) and ^{13}C NMR (100 MHz, CD_3COCD_3) data in ◉ **Table 1**.

(βR)-2,2′,5′,β-Tetrahydroxy-4-methoxydihydrochalcone (**3**): yellow white amorphous powder. $[\alpha]_D^{16.6}$ − 18.82 (*c* 0.13, MeOH); UV (MeOH) λ_{max} (log ε): 224 (4.45), 256 (3.89), 282 (3.81), 354 (3.58) nm; IR (KBr) ν_{max}: 3405, 3387, 3283, 3080, 3025, 2920, 2874, 2845, 1736, 1672, 1611, 1513, 1463, 1435, 1301, 1261, 1218, 1201, 1182, 1163, 1035, 892, 842, 795 cm^{-1}; EI-MS *m/z* (%): 304 $[M]^+$ (4), 286 (5), 269 (55), 268 (100), 150 (32); HR-EI-MS *m/z*: 304.0995 $[M]^+$ (calcd. for $C_{16}H_{16}O_6$, 304.0947); ^1H NMR (400 MHz, CD_3OD) and ^{13}C NMR (100 MHz, CD_3OD) data in ◉ **Table 1**.

Schistosomicidal assay

A schistosomicidal assay was performed according to a previous method [16,17] (detailed procedure listed in Supporting Information).

DPPH free radical scavenging capability assay

Antioxidant activity was tested by the DPPH method, which has been previously described [18] (detailed procedure see Supporting Information).

Supporting information

Detailed protocols for the schistosomicidal assay and DPPH free radical scavenging capability assay, spectroscopic data, and physicochemical properties of **4** and **5**, as well as 1D and 2D NMR, IR, UV, and MS spectra of **1**–**3** are available as Supporting Information.

Acknowledgements

This research was financially supported by the National Natural Science Foundations of China (No. 31170313), as well as the program of "Reserve Talents of the Young Academy and Technology Leaders in Yunnan Province" (No. 2008PY005). We are grateful to Prof. Yi-Mei Yang (Dali University, China) for kindly providing *S. japonicum* worms from rabbit hosts, and to Associate Prof. Xiao-Bo Liu (Dali University, China) for his experiment guidance. We appreciate the kind help of Ling-Yun Jiang with information retrieval as well.

Conflict of Interest

The authors declare no conflict of interest.

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