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Isolation and identification of phytochemical constituents from the fruits of *Acanthopanax senticosus*

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Phytochemical constituents were isolated from the fruits of *Acanthopanax senticosus* by repeated chromatography and prep-HPLC. Their structures were identified as β-sitosterol (1), daucosterol (2), *p*-hydroxybenzoic acid (3), vanillic acid (4), uracil (5), eleutheroside K (6), songoroside A (7), copteroside B (8) and *myo*-inositol (9) by spectroscopic analysis. Among them, *p*-hydroxybenzoic acid (3), eleutheroside K (6) and songoroside A (7) were isolated for the first time from the fruits of *A. senticosus*, and songoroside A (7) was isolated for the first time from *Acanthopanax* species.

Key words: *Acanthopanax senticosus*, Araliaceae, repeated chromatography, songoroside A.

INTRODUCTION

Acanthopanax senticosus (Araliaceae) is a deciduous perennial shrub species which is distributed in Korea, China, Japan and Russia. The herb grows in mixed and coniferous mountain forests forming low undergrowth or is found in groups in thickets. *A. senticosus* is broadly tolerant of soil type, growing in sandy, loamy, and heavy clay soils with acid, neutral, or alkaline chemistry, including soils of low nutritional value. *A. senticosus* grows to 2 ~ 3 m in height. The stem bark is gray-brown, the stem is long, covered with thin thorns, and bears five leaflets and umbel-shaped flowers that can be in July in most habitats (Perry and Metgen, 1980; Yook, 1990). The medicinal uses of *A. senticosus*, present in all parts of the plant include anti-bacterial, anti-cancer, anti-inflammatory, anti-gout, anti-hepatitis, anti-hyperglycemic, anti-leishmanicidic, anti-oxidant, anti-pyretic, choleretic, hemostatic, anti-xanthine oxidase, immunostimulatory, hypo-cholesterolemic, radio-protectant (Davydov and

Krikorian, 2000), anti-microbial (Lee et al., 2004a; Kim et al., 2006) and inhibition against irradiation-induced injury in rats (Li and Zhou, 2007). The phytochemicals of *A. senticosus* are composed of lignans (eleutheroside E, syringaresinol, and sesamin) (Ryu et al., 2004), terpenoids (chiisanogenin, chiisanoside, isochiisanoside, and oleanolic acid) (Yook et al., 1991; Park et al., 2000; Lee et al., 2003), phenolic compounds (eleutheroside B, chlorogenic acid, and caffeic acid) (Bladt et al., 1990; Nishibe et al., 1990), coumarins (isofraxidin and isofraxidin-7-*O*-β-D-glucoside) (Wagner et al., 1982; Bai et al., 2011), and flavonoids (hyperin, rutin, quercetin, and quercitrin) (Chen et al., 2002; Lee et al., 2003; Xiaoguang et al., 2007).

There are many reports on the analysis of phytochemicals in *A. senticosus* (Row and Song, 2004; Lee et al., 2004b; Apers et al., 2005; Kim et al., 2006; Li et al., 2006; Ma et al., 2011). There have been many reports on the medicinal effects, isolation, and identification of compounds from the roots, stems and leaves of *A. senticosus*. However, there have been few investigations of the fruits of *A. senticosus*. Therefore, this research is focused on the isolation and identification of

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compounds from *A. senticosus* fruits by repeated chromatography and recycling preparative high performance liquid chromatography (prep-HPLC).

MATERIALS AND METHODS

Plant materials

The fruits of *A. senticosus* (Araliaceae) were collected at Gongju and verified by Prof. Seon Haeng Cho, Gongju National University of Education, Republic of Korea. A voucher specimen (No. LEE 2008-01) was deposited at the Herbarium of Department of Integrative Plant Science, Chung-Ang University, Republic of Korea.

General experimental procedures

Electron ionization mass spectrometry (EI-MS) was measured with a Jeol JMS-600 W (Tokyo, Japan) mass spectrometer. ^{1}H- and ^{13}C-nuclear magnetic resonance (NMR) spectra were recorded with a Bruker Avance 300 or 500 NMR (Rheinstetten, Germany) spectrometers in $CDCl_3$, C_5D_5N, DMSO or CD_3OD using tetra methyl silane (TMS) as an internal standard. Chemical shifts were reported in parts per million (δ) and coupling constants (*J*) were expressed in Hertz (Hz). Thin layer chromatography (TLC) analysis was conducted with Kiesel gel 60 F254 (Art. 5715, Merck Co., Germany) plates (silica gel, 0.25 mm layer thickness), with compounds visualized by spraying with 10% H_2SO_4 in MeOH. Repeated chromatography was conducted with a silica gel (200 to 400 mesh ASTM; Merck Co., Germany). All other chemicals and reagents were analytical grade. Prep-HPLC was conducted by a JAI LC-9104 (Tokyo, Japan) system equipped with an L-6050 pump and UV-3702 UV/VIS detector.

Extraction and isolation

The dried fruits of *A. senticosus* (3.0 kg) were ground into powder and extracted with methanol (MeOH, 10 L × 3) under reflux. The resultant extracts were combined and concentrated under reduced pressure to afford 594.2 g of the residue. The MeOH extract (594.2 g) was suspended in water (H_2O) and then partitioned successively with equal volumes of chloroform ($CHCl_3$, 34.6 g), ethyl acetate (EtOAc, 44.4 g) and *n*-butanol (*n*-BuOH, 87.0 g). A portion of the $CHCl_3$ fraction was chromatographed on a silica gel column eluted in a gradient of *n*-hexane - EtOAc (97:3 and 30:70) to afford compounds 1 and 2, respectively. A portion of the EtOAc fraction was chromatographed on a silica gel column eluted in a gradients of *n*-hexane and EtOAc (100% *n*-hexane up to 100% EtOAc) and EtOAc and MeOH (100% EtOAc up to 100% MeOH) to afford 9 subfractions (E_1 to E_9). Subfraction E_4 (*n*-hexane:EtOAc = 85:15) was analyzed by prep-HPLC using a JAIGEL-GS column with UV/VIS detection set at 240 nm and a mobile phase of $CHCl_3$-MeOH-H_2O (80:20:2) at ambient temperature to afford compounds 3 (t_R 47 min) and 4 (t_R 58 min). Subfraction E_6 (*n*-hexane:EtOAc = 35:65) was rechromatographed on a silica gel (No. 7729) column eluted in a gradient of $CHCl_3$ and MeOH (90:10) to afford compound 5. Subfraction E_7 was rechromatographed on a silica gel (No. 7729) column eluted in a gradient of $CHCl_3$ and MeOH (80:20 and 70:30) to afford compounds 6 and 7, respectively. Subfraction E_8 (*n*-hexane:EtOAc = 5:95) was rechromatographed on a Sephadex LH-20 eluted in MeOH to obtain compound 8. A portion of the *n*-BuOH fraction was chromatographed on a silica gel column eluted in a gradient of $CHCl_3$ and MeOH (80:20) to afford compound 9.
Compound 1 – white powder; EI-MS m/z: 414 [M]$^+$ (100.0), 396 (42.5), 381 (21.8), 329 (25.0), 303 (28.9), 289 (4.0), 273 (25.3), 255 (48.0), 231 (15.9), 213 (25.2), 159 (25.6), 145 (25.8); ^{1}H- and ^{13}C-NMR (300 MHz, $CDCl_3$): Table 1.
Compound 2 – white powder; FAB-MS m/z: 577 [M + H]$^+$; ^{1}H- and ^{13}C-NMR (300 MHz, C_5D_5N): Table 1.
Compound 3 – white powder; EI-MS m/z: 138 [M]$^+$ (92.9), 121 (100.0), 93 (23.7), 81 (3.8), 65 (12.6); ^{1}H- and ^{13}C-NMR (300 MHz, DMSO): Table 2.
Compound 4 – white powder; EI-MS m/z: 168 [M]$^+$ (100.0), 153 (33.1), 137 (93.5), 125 (10), 109 (21), 81 (9); ^{1}H- and ^{13}C-NMR (500 MHz, DMSO): Table 2.
Compound 5 – white powder; EI-MS m/z: 112 [M]$^+$ (100), 69 (52); ^{1}H-NMR (300 MHz, CD_3OD): δ 7.41 (1H, d, *J* = 7.8 Hz, H-6), 5.63 (1H, d, *J* = 7.8 Hz, H-5).
Compound 6 – amorphous powder; FAB-MS m/z: 735 [M + H]$^+$; ^{1}H- and ^{13}C-NMR (500 MHz, C_5D_5N): Table 3.
Compound 7 – amorphous powder; FAB-MS m/z: 589 [M + H]$^+$; ^{1}H- and ^{13}C-NMR (500 MHz, C_5D_5N): Table 3.
Compound 8 – amorphous powder; FAB-MS m/z: 649 [M + H]$^+$; ^{1}H- and ^{13}C-NMR (500 MHz, C_5D_5N): Table 3.
Compound 9 – brown powder; EI-MS m/z: 144 [M-2H_2O]$^+$ (11.6), 115 (1.7), 102 (32.1), 91 (9.4), 73 (100.0), 60 (27.1); ^{1}H-NMR (300 MHz, DMSO): δ 4.58 (1H, d, *J* = 4.2 Hz, OH), 4.52 (1H, d, *J* = 4.2 Hz, OH), 4.38 (H, d, *J* = 5.7 Hz, OH), 3.11 (2H, m, CH), 3.00 (1H, m, CH); ^{13}C-NMR (75 MHz, DMSO): δ 75.6 (C-2), 74.6 (C-5), 73.1 (C-1,3), 72.2 (C-4,6).

RESULTS AND DISCUSSION

A chromatographic separation of the MeOH extract of *A. senticosus* led to the isolation of compounds 1 to 9 (Figure 1). Compounds 1 and 2 were obtained as white powders from the $CHCl_3$ fractions. ^{1}H-NMR spectra of 1 and 2 showed the existence of a sterol skeleton and a molecular ion peak at m/z 414 [M]$^+$ in the EI-MS and 577 [M + H]$^+$ in the FAB-MS. Two angular methyl singlets of H-18 and -19 at δ 0.67 to 0.68 and 0.94 to 1.01 and three doublets of H-21, -26 and -27 at δ 0.92 to 1.00, 0.81 to 0.94 and 0.86 to 0.89 were observed, respectively. An olefinic proton signal of H-6 was observed at δ 5.35. ^{13}C-NMR spectra of compounds 1 and 2 showed 29 and 35 resonances, respectively. C-5 and -6 signals of compounds 1 and 2 were observed at δ 141.0 to 141.3 and 121.9 to 122.3, respectively. Compounds 1 and 2 had similar structural signals. The typical pattern of a glucose moiety was observed in the ^{1}H- and ^{13}C-NMR spectra in compound 2. The anomeric proton of compound 2 produced a peak at δ 5.09 (d, *J* = 6.9 Hz), and the glucose position was at C-3 (β-linkage) of the aglycone according to HMBC analysis.

Accordingly, the structures of compounds 1 and 2 were elucidated as β-sitosterol (stigmast-5-en-3-ol) and daucosterol (β-sitosterol-3-*O*-β-D-glucoside), respectively, by comparison of the spectral data, as described in the literature (Umlauf et al., 2004; Park et al., 2009; Yang et al., 2009; Lee et al., 2011; Zhang et al., 2011). In previous papers, β-sitosterol, the most common plant sterol has been reported to have anti-inflammatory, anti-tumor and anti-microbial activities (Park et al., 2001; Yuk et al., 2007; Xu et al., 2011). Daucosterol, a β-sitosterol glycoside induces a protective Th1 immune response

Table 1. ^{1}H- and ^{13}C-NMR spectral data for compounds 1 and 2.

No.	1		2	
	δ_H	δ_C	δ_H	δ_C
1	-	37.4	-	37.3
2	-	31.8	-	29.4
3	3.52 (m)	71.9	-	78.5
4	2.27 (m)	42.4	-	38.4
5	-	141.0	-	141.3
6	5.35 (m)	121.9	5.35 (m)	122.3
7	-	32.0	-	31.8
8	-	32.0	-	30.6
9	-	50.3	-	50.7
10	-	36.7	-	36.8
11	1.99 (m)	21.2	-	20.4
12	-	39.8	-	40.3
13	-	42.4	-	42.7
14	-	57.0	-	56.9
15	-	24.5	-	23.8
16	-	28.4	-	26.7
17	-	56.1	-	56.6
18	0.68 (s)	12.0	0.67 (s)	12.4
19	1.01 (s)	19.1	0.94 (s)	19.6
20	-	36.3	-	34.5
21	0.92 (d, 6.3)	18.9	1.00 (d, 6.3)	19.4
22	-	34.1	-	32.6
23	-	26.2	-	24.9
24	-	46.0	-	46.4
25	-	29.1	-	28.9
26	0.81 (d, 6.3)	19.1	0.94 (d, 5.4)	19.8
27	0.86 (d, 4.2)	19.6	0.89 (d, 6.3)	20.1
28	-	23.2	-	21.7
29	0.80 (t, 5.8)	12.1	0.87 (m)	12.5
Glc				
1			5.09 (d, 6.9)	103.0
2				75.8
3				79.0
4				72.1
5				78.9
6				63.2

Chemical shifts are reported in parts per million (δ), and coupling constants (J) are expressed in Hertz.

against disseminated candidiasis (Lee et al., 2007).

Compounds 3 and 4 were obtained as white powders from the EtOAc fraction and showed molecular ion peaks at m/z 138 [M]$^+$ and 168 [M]$^+$ in the EI-MS, respectively. The ^{1}H-NMR spectra of compounds 3 and 4 showed phenolic compound signals. The only differences between compounds 3 and 4 are the typical A_2B_2 and ABX types in the benzene ring. In the ^{1}H-and ^{13}C-NMR spectra of compound 3, two doublets of aromatic proton signals at δ 7.78 (J = 8.7 Hz) and 6.81 (J = 9.0 Hz), four aromatic carbon signals at δ 115.2, 121.5, 131.6, 161.6, and one carboxyl carbon signal at δ 167.3 were observed. In addition, two doublets and one double doublet of aromatic proton signals at δ 7.35 (J = 1.8, 8.0 Hz), 7.06 (J = 1.8 Hz) and 6.61 (J = 8.0 Hz) were observed in compound 4.

Accordingly, the structures of compounds 3 and 4 were identified as *p*-hydroxybenzoic acid and vanillic acid,

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

No.	3		4	
	δ_H	δ_C	δ_H	δ_C
1	-	121.5	-	123.8
2	7.78 d (8.7)	131.6	7.06 d (1.8)	114.3
3	6.81 d (9.0)	115.2	-	149.2
4	-	161.6	-	153.3
5	6.81 d (9.0)	115.2	6.61 d (8.0)	116.1
6	7.78 d (8.7)	131.6	7.35 dd (1.8, 8.0)	126.0
COOH	-	167.3	-	170.8
OMe			3.76 s	57.0

Chemical shifts are reported in parts per million (δ), and coupling constants (J) are expressed in Hertz.

Table 3. ^{1}H and ^{13}C-NMR spectral data of compounds 6 to 8.

No.	6		7		8	
	δ_H	δ_C	δ_H	δ_C	δ_H	δ_C
1		39.4		39.2		39.2
2		27.0		27.0		26.5
3	3.27 (dd, 4.2, 11.7)	89.3	3.31 (br d, 10.8)	89.5	3.31 (br d, 6.5)	79.9
4		40.0		40.0		44.0
5		56.4		56.3		48.0
6		19.0		19.0		18.8
7		33.7		33.7		33.4
8		40.2		40.2		40.3
9		48.5		48.5		48.6
10		37.5		37.5		37.4
11		24.2		24.3		24.4
12	5.50 (t-like, 3.2)	123.0	5.47 (t-like)	123.0	5.47 (t-like)	123.1
13		145.3		145.3		145.4
14		42.6		42.5		42.5
15		28.8		28.8		28.8
16		24.3		24.3		24.3
17		47.0		47.0		47.2
18		42.7		42.7		42.7
19		47.2		47.2		46.9
20		31.4		31.5		31.4
21		34.7		34.8		34.8
22		33.7		33.8		33.8
23	1.32 (s)	28.6	1.33 (s)	28.8		64.9
24	0.98 (s)	17.5	0.97 (s)	17.5	0.93 (s)	14.2
25	0.85 (s)	16.0	0.78 (s)	16.0	0.91 (s)	16.6
26	1.09 (s)	17.9	1.02 (s)	17.9	1.02 (s)	18.0
27	1.20 (s)	26.7	1.33 (s)	26.7	1.27 (s)	26.8
28		180.7		180.7		180.9
29	0.99 (s)	33.8	0.99 (s)	33.8	0.94 (s)	33.8
30	1.02 (s)	24.3	1.02 (s)	24.3	1.00 (s)	24.2

respectively, by comparison of the spectral data, as described in the literature (Shimizu et al., 1983; Pyo et al., 2002; González-Baró et al., 2008; Zhang et al., 2011; Yuan et al., 2012). *p*-Hydroxybenzoic acid shows antioxidant activity on DPPH radical assay and the inhibition of lipoperoxidation (Yamaguchi et al., 2006). Vanillic acid is

Table 3. Contd.

No.	6		7		8	
	δ_H	δ_C	δ_H	δ_C	δ_H	δ_C
Ara						
1	4.93 (d, 5.3)	105.3				
2		76.4				
3		74.6				
4		72.9				
5		65.2				
Rha						
1	6.17 (br s)	102.3				
2		74.3				
3		73.1				
4		70.4				
5		69.2				
6	1.66 (d, 6.2)	19.0				
Xyl						
1			5.05 (d, 5.3)	107.3		
2				76.0		
3				78.9		
4				74.4		
5				68.0		
GluA						
1					5.23 (d, 7.8)	105.0
2						76.9
3						79.0
4						74.3
5						75.1
6						175.0

Chemical shifts are reported in parts per million (δ), and coupling constants (J) are expressed in Hertz.

a phenolic derivative of edible plants and fruits and has antibacterial and antimicrobial properties against *Listeria monocytogenes*, *Listeria innocua*, *Listeria grayi* and *Listeria seeligeri* (Rai and Maurya, 1966; Delaquis et al., 2005).

Compound 5 was obtained as white powder from the EtOAc fraction and showed a molecular ion peak at m/z 112 [M]$^+$ in the EI-MS. In the ^{1}H-NMR spectrum of compound 5, two doublets of typical olefinic proton signals at δ 7.41 (*J* = 7.8 Hz) and 5.63 (*J* = 7.8 Hz) were observed. Accordingly, the structure of compound 5 was elucidated as uracil by comparison of the spectral data, as described in the literature (Lee et al., 2002). Uracil can be used to determine microbial contamination of tomatoes as its presence is an indication of lactic acid bacteria contamination in the fruit (Hidalgo et al., 2005). Compounds 6 to 8 were obtained as amorphous powders from the EtOAc fraction and showed molecular ion peaks

at m/z 735 [M+H]$^+$, 589 [M+H]$^+$ and 649 [M+H]$^+$ in the FAB-MS, respectively. The aglycone of compounds 6 and 7 was oleanolic acid, while that of compound 8 was hederagenin. In the ^{1}H-NMR spectra of compounds 6 to 8, one olefinic proton signal at δ 5.47-5.50 (H-12) and one oxygen-bearing methine proton signal at δ 3.27-3.31 (H-3) were observed. Seven tertiary methyl group signals at δ 0.78 to 1.33 (each s, H-23, 24, 25, 26, 27, 29 and 30) were observed in compounds 6 and 7. In addition, six tertiary methyl groups signals at δ 0.91 to 1.27 (each s, H-24, 25, 26, 27, 29 and 30) were observed in compound8.

In the ^{13}C-NMR spectra of compounds 6 to 8, two sp^2 carbons at δ 123.0 to 123.1 (C-12) and 145.3 to 145.4 (C-13) and one ester carboxyl group at δ 180.7 to 180.9 (C-28) were observed. The chemical shift of the oxygen-bearing carbon signal was observed at δ 89.5, 89.3 and 79.9 (C-3), suggesting that sugar moieties were attached.
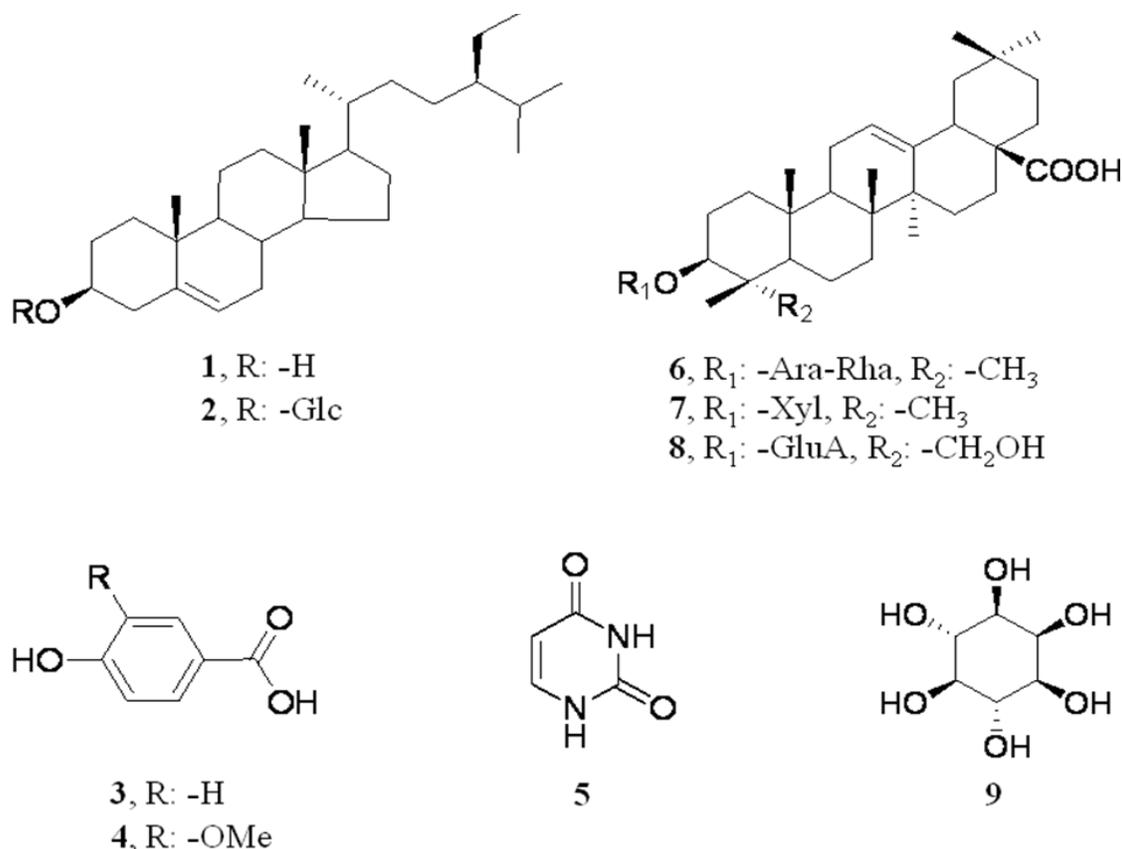
Figure 1. Structures of compounds 1 to 9.

In the ^{1}H-NMR spectrum of compound 6, anomeric protons of δ 4.93 (d, J = 5.3 Hz, H-1 of Ara) and 6.17 (br s, H-1 of Rha) were observed. Identification of the correlation between δ 4.93 (H-1 of Ara) and δ 89.3 (C-3), and δ 6.17 (H-1 of Rha) and δ 76.4 (Ara-2) by HMBC indicated that an α-L-rhamnosyl-(1→2)-α-L-arabinoside moiety was linked to C-3 of the aglycone of compound 6. Compound 7 showed one anomeric proton signal at δ 5.05 (d, J = 5.3 Hz, H-1 of Xyl). Identification of the correlation between δ 5.05 (H-1 of Xyl) and δ 89.5 (C-3) by HMBC indicated that a β-D-xyloside moiety was linked to C-3 of the aglycone of compound 7. Compound 8 showed one anomeric proton signal at δ 5.23 (d, J = 7.8 Hz, H-1 of GluA). Identification of the correlation between δ 5.23 (H-1 of GluA) and δ 79.9 (C-3) by HMBC indicated that a β-D-glucuronic acid moiety was linked to C-3 of the aglycone of compound 8. Due to the upfield shift of C-3, aglycone C-23 was indicative of a substitution by CH_2OH. ^{13}C-NMR spectra of compounds 6, 7 and 8 showed 41, 35 and 36 resonances, respectively.

Accordingly, the structures of compounds 6 to 8 were identified as eleutheroside K, songoroside A and copteroside B, respectively, by comparison of the spectral data, as described in the literature (Saluja and Santani, 1986; Akimailiev et al., 1988; Shao et al., 1989; Majester-Savornin et al., 1991; Alabdul Magid et al., 2006).

Eleutheroside K, songoroside A and copteroside B have anti-leishmanial activity, anti-inflammatory effects and inhibitory activity toward pancreatic lipase (Dai et al., 1989; Delmas et al., 2000; Li et al., 2007).

Compound 9 was obtained as a brown powder from the *n*-BuOH fraction. Three hydroxyl proton signals at δ 4.58, 4.52, and 4.38 and two multiplets of CH proton signals at δ 3.11 and 3.00 were observed. The ^{13}C-NMR spectrum of compound 9 showed four ring carbon signals at δ 75.6, 74.6, 73.1 and 72.2. Accordingly, the structure of compound 9 was elucidated as *myo*-inositol by comparison of the spectral data, as described in the literature (Yasue et al., 1968). A previous placebo-controlled study has demonstrated that *myo*-inositol supplementation improves features of dysmetabolic syndrome in post-menopausal women, including triglycerides, HDL cholesterol and diastolic blood pressure (Giordano et al., 2011).

In conclusion, nine compounds, β-sitosterol (1), daucosterol (2), *p*-hydroxybenzoic acid (3), vanillic acid (4), uracil (5), eleutheroside K (6), songoroside A (7), copteroside B (8) and *myo*-inositol (9) were isolated from the fruits of *A. senticosus*. To the best of our knowledge, this is the first report on the isolation of *p*-hydroxybenzoic acid (3), eleutheroside K (6), and songoroside A (7) from the fruits of *A. senticosus*, and songoroside A (7) from

Acanthopanax species.

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