J Korean Soc Appl Biol Chem (2015) 58(3):365–371
DOI 10.1007/s13765-015-0051-9

Online ISSN 2234-344X
Print ISSN 1738-2203

ARTICLE

Plant-derived molecules from *Saussurea grandifolia* as inhibitors of aldose reductase

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Received: 1 January 2015 / Accepted: 7 February 2015 / Published online: 24 February 2015

Abstract *Saussurea grandifolia* was tested for aldose reductase (AR) inhibition as part of a search for potentially therapeutic natural compounds. Stepwise polarity fractions were tested for in vitro inhibition of rat lens AR. Of these, the ethyl acetate (EtOAc) and *n*-butanol (*n*-BuOH) fractions exhibited AR inhibitory activities. A chromatographic separation of the active EtOAc and *n*-BuOH fractions led to the isolation of nine compounds, which were known and identified as vitexin (**1**), genkwanin-5-*O*-glucoside (**2**), vitexin 2″-*p*-hydroxybenzoate (**3**), kaempferol-3-*O*-rutinoside (**4**), isovitexin (**5**), quercitrin (**6**), isoquercitrin (**7**), 1,5-di-*O*-caffeoylquinic acid (**8**), and vicenin 1 (**9**). Among these compounds, compounds **6**, **7**, and **8** showed very strong inhibitory activities against AR (IC_{50}'s = 0.34, 0.32, and 0.08 μM, respectively). The results suggest that *S. grandifolia* is clearly a potential source for therapeutic agent that might be useful for the treatment of diabetic complications.

Keywords *Saussurea grandifolia* · Aldose reductase · Flavonoid · Phenylpropanoid

Introduction

The term "mountain vegetables" refers to edible plants that grow naturally in the wild and are not grown and harvested from fields. Mountain vegetables may have medical properties and are some of the most promising agricultural crops in Korea. Interest in mountain vegetables is gradually increasing as people become more concerned about their health (Lee et al. 2011). Mountain vegetables belonging to the family Compositae are used for their leaves and referred to as "mountain-namul" in Korea. Chwinamul is a well-known Korean mountain-namul and includes several species: *Aster scaber*, *Aster yomena*, *Solidago virga* var. *gigantea*, *Solidago virgaaurea* var. *asiatica*, *Saussurea grandifolia*, *Ainsliaea acerifolia*, *Ligularia fischeri*, and *Ligularia stenocephala*. Among them, *Saussurea* is a genus of about 300 species of flowering plants native to the cool temperate and arctic regions of Asia, Europe, and North America, with the highest diversity found in alpine habitats in the Himalayas and central Asia (Nugroho et al. 2009; Park 2010).

Saussurea grandifolia is a perennial herbaceous plant ranging in height from 30 to 50 cm tall. The leaves are produced in a dense basal rosette spiraling up the flowering stem. The flower blooms between July and October and forms a dense head of small capitula, often completely surrounded by dense white to purple woolly hairs. The individual florets are also white to purple (Lee et al. 2005a, b, c). Investigation of the phytochemical constituents and bioactivities of *Saussurea* species has revealed the presence of many interesting bioactive compounds with antioxidant, anticancer, and anti-atherosclerotic activities, such as terpenoids (Shi 2008), flavonoids (Jiang et al. 2004), lignans (Takasaki et al. 2000; Ko et al. 2004), sesquiterpene lactones (Yang et al. 2004), and γ-linolenic acid (Tsevegsuren et al. 1997). However, few studies of the phytochemical constituents of *S. grandifolia* have been conducted.

Aldose reductase (AR) is a rate-limiting enzyme in the polyol pathway associated with the conversion of glucose to sorbitol. The enzyme is located in the eye, kidney, myelin sheath, and other tissues that are less affected by diabetic complications (Narayanan 1993). In a diabetic

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condition, sufficient glucose can enter the tissues, and the pathway operates to produce both sorbitol and fructose. These abnormal metabolic results have been reported to be responsible for diabetic complications such as cataracts, retinopathy, neuropathy, and nephropathy (Kato et al. 2009). AR inhibitors can prevent or reverse early-stage diabetic complications.

The present study was designed to isolate AR inhibitory compounds from *S. grandifolia* as Ksorean edible mountain vegetables.

Materials and methods

Plant materials

The aerial parts of *S. grandifolia* Maximowicz (Compositae) were collected at Ulleung Island, Republic of Korea (Fig. 1). The specimen was botanically authenticated by the Korea National Arboretum, Republic of Korea. A voucher specimen (No. LEE 2011-02) was deposited at the Herbarium of the Department of Integrative Plant Science, Chung-Ang University, Republic of Korea.

Fig. 1 Aerial parts of *S. grandifolia*

Instruments and reagents

n-Hexane, methylene chloride (MC), chloroform ($CHCl_3$), ethyl acetate (EtOAc), *n*-butanol (*n*-BuOH), methanol (MeOH), dimethyl sulfoxide-d_6 (DMSO-d_6), and distilled water (J. T. Baker®, USA) were used as solvents. Reagents such as DL-glyceraldehyde, nicotinamide adenine dinucleotide 2′-phosphate (β-NADPH), sodium phosphate buffer, and potassium phosphate buffer were used. Open column chromatography was conducted using silica gel (200–400 mesh ASTM; Merck Co., Germany), ODS gel (12 nm, S-150 μm; YMC Co., Japan), and Sephadex LH-20 (100-100G; Sigma-Aldrich Co., USA). Optical rotation was measured in MeOH using a Jasco P-1020 polarimeter (Tokyo, Japan). Mass spectrometry (MS) was measured using 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 500 NMR (Rheinstetten, Germany) spectrometer using tetramethylsilane (TMS) as an internal standard. Evaporation was conducted using an Eyela rotary evaporator system (Tokyo, Japan) under reflux *in vacuo*. Recycling preparative HPLC was conducted using a Jai LC-9014 system (Tokyo, Japan), and determination was performed using an L-6050 system pump with a UV-3702 system UV/VIS detector and an FC-339 fraction collector. Thin layer chromatography (TLC) was conducted with Kiesel gel 60 F_{254} (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 followed by charring at 100 °C.

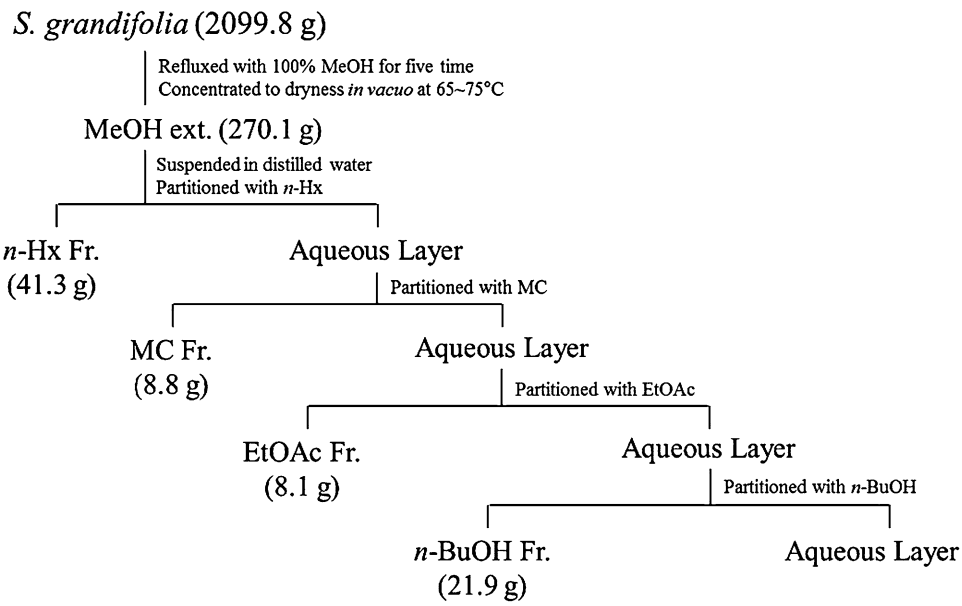


Fig. 2 Extraction and fractionation of *S. grandifolia*

Extraction, fractionation, and isolation

The dried and powdered aerial parts of *S. grandifolia* (2099.8 g) were extracted with MeOH (7 L × 5) under reflux at 65–75 °C. The filtrate was concentrated to dryness (270.1 g) *in vacuo*, suspended in water (H_2O), and then partitioned successively using *n*-hexane (41.3 g), MC (8.8 g), EtOAc (8.1 g), and *n*-BuOH (21.9 g) (Fig. 2).

A portion of the EtOAc fraction (8.1 g) was chromatographed on a silica gel (No. 7734) using a stepwise $CHCl_3$–MeOH (100 % $CHCl_3$ up to 100 % MeOH) solvent system, which yielded 11 sub-fractions. MeOH recrystallization of sub-fraction 7 (2.5 g) yielded **1** (7.2 mg). Sub-fraction 7 was separated using a Sephadex LH-20 column with 100 % MeOH to give fractions 7-a–7-f. Compound **2** (5.3 mg) was separated from fraction 7-d (70 mg) by recrystallization. Separation of sub-fraction 8 (0.5 g) using a Sephadex LH-20 (100 % MeOH) yielded seven fractions (8-A–8-g). A portion of fraction 8-d (90 mg) was separated using a Sephadex LH-20 and a prep-LC (MeOH:H_2O = 8:2, flow rate: 4 mL/min, UV 256 nm), which yielded **3** (2.8 mg) from fraction 8-d-4 (20 mg). Fraction 9 (1.1 g) was applied to a Sephadex LH-20 gel with a gradient of 100 % MeOH to 90 % MeOH in H_2O, which yielded seven fractions (9-a–9-g). Fraction 9-c (0.17 g) was separated using a Sephadex LH-20 (MeOH:H_2O = 6:4), which yielded eight fractions (9-c-1–9-c-8). Fractions 9-c-3 (20 mg), 9-c-4 (24 mg), and 9-c-7 (13 mg) were subjected to several rounds of a prep-LC using a mixture of MeOH:H_2O (8:2 and 9:1) to yield **4** (2.7 mg), **5** (3.4 mg), and **6** (1.9 mg), respectively. Fraction 9-d (0.11 g) was separated using an ODS gel column (60 % MeOH in H_2O) to yield **7** (3.1 mg) as a yellow powder. Fraction 10 (1.0 g) was separated by a Sephadex LH-20 column using MeOH:H_2O (2:1) to give fractions 10-a–10-h. MeOH recrystallization of fraction 10-d (0.13 g) yielded **8** (10.8 mg).

The *n*-BuOH fraction (21.9 g) was separated using a silica gel column (6 × 80 cm, No. 7734) with a gradient of $CHCl_3$–MeOH (100 % $CHCl_3$ up to 100 % MeOH) to yield 17 subfractions. Sub-fraction 12 (1.1 g) was separated by a Sephadex LH-20 column using a 100 % MeOH isocratic system, yielding seven fractions (12-a–12-g). Fraction 12-f (30 mg) was separated using a prep-LC, and four fractions (12-f-1–12-f-4) were collected after elution with MeOH and H_2O (8:2). Fraction 12-f-3 (10 mg) was separated by an ODS gel column chromatography using an eluent of 60 % MeOH in H_2O. Fraction 12-f-3-b (7 mg) was further purified by a prep-LC (MeOH:H_2O = 9:1), which yielded **9** (2.1 mg).

Measurement of AR activity

Lenses were removed from the eyes of Sprague–Dawley rats (weighing 250–280 g), placed in 0.5 mL sodium buffer per lens, and preserved until use by freezing. For experiments, the rat lenses were homogenized and centrifuged at 10,000 rpm (4 °C, 20 min), and the supernatant was used as the enzyme source. AR activity was determined spectrophotometrically by measuring the decrease in the absorption of β-NADPH at 340 nm for a 4 min period at room temperature in a quartz cell with DL-glyceraldehydes as substrate (Sato and Kador 1990). The assay mixture contained 0.1 M potassium phosphate buffer (pH 7.0), 0.1 M sodium phosphate buffer (pH 6.2), 1.6 mM β-NADPH, and test samples (in DMSO), with 0.025 M DL-glyceraldehyde as substrate. IC_{50} is the concentration of inhibitor that gives a 50 % inhibition in enzyme activity. IC_{50} values were calculated from the least-squares regression line of the log of concentration plotted against the percentage decrease in the measured absorbance. 3,3-tetramethylene glutaric acid (TMG), a typical AR inhibitor, was used as a positive control. A negative control was prepared using DMSO.

Results and discussion

AR activities of the extracts and fractions of *S. grandifolia*

The results of the test of the MeOH extract and fractions of *S. grandifolia* are summarized in Table 1. The MeOH

Table 1 IC_{50} values of the extract and fractions on AR inhibition

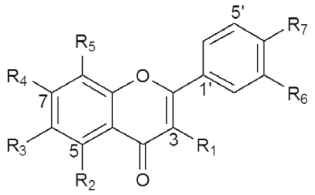
Sample	Concentration (μg/mL)	Inhibition[a] (%)	IC_{50}^{b} (μg/mL)
MeOH extract	5	85.19	0.84
	1	56.64	
	0.5	37.16	
n-Hexane fraction	10	21.58	–
MC fraction	10	46.48	–
EtOAc fraction	1	93.41	0.12
	0.1	57.21	
	0.05	24.37	
n-BuOH fraction	10	84.07	3.33
	5	67.28	
	1	8.67	
TMG[c]	5	78.48	0.96
	1	58.96	
	0.5	32.16	

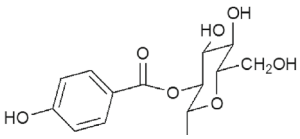
[a] Inhibition rate was calculated as a percentage with respect to the control value

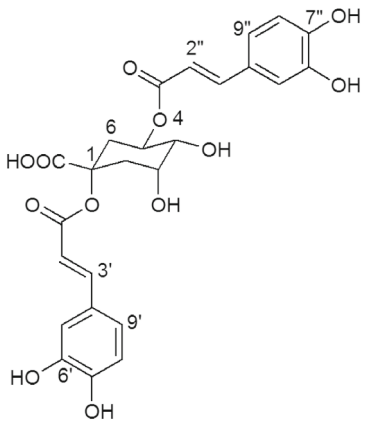
[b] IC_{50} value was calculated from least-squares regression analysis of the plot of the logarithm of three graded concentrations versus % inhibition

[c] TMG was used as a positive control

Fig. 3 Structures of compounds **1–9**



Compound	R_1	R_2	R_3	R_4	R_5	R_6	R_7
1	H	OH	H	OH	*C*-Glc	H	OH
2	H	*O*-Glc	H	OMe	H	H	OH
3	H	OH	H	OH		H	OH
4	*O*-Rut	OH	H	OH	H	H	OH
5	H	OH	*C*-Glc	OH	H	H	OH
6	*O*-Rham	OH	H	OH	H	OH	OH
7	*O*-Glc	OH	H	OH	H	OH	OH
9	H	OH	*C*-Xyl	H	*C*-Glc	H	OH



extract of *S. grandifolia* inhibited rat lens AR with an $IC_{50} = 0.84$ μg/mL. The stepwise polarity fractions of the MeOH extract of *S. grandifolia* were tested for AR inhibitor activity. The IC_{50} value of the EtOAc fraction had stronger activity than TMG, which is a very strong AR inhibitor. There have been few reports regarding the biological activities of the MeOH extract of *S. grandifolia*. Our results demonstrate that the MeOH extract and the EtOAc fraction of *S. grandifolia* show strong inhibitory effects on rat lens AR (Table 1).

Identification of compounds **1–9** from *S. grandifolia*

Chromatographic separation of the active EtOAc and *n*-BuOH fractions led to the isolation of eight flavonoids and a phenylpropanoid (Fig. 3). The known compounds, vitexin (**1**) (Kim et al. 2005; Zhou et al. 2005), genkwanin-5-*O*-glucoside (**2**) (O'Rourke et al. 2005; Park et al. 2006), vitexin 2″-*p*-hydroxybenzoate (**3**) (Park et al. 2006; Gaffield 1978), kaempferol-3-*O*-rutinoside (**4**) (Wang et al. 1999; Abraham et al. 2008), isovitexin (**5**) (Peng et al. 2005; Song et al. 2008), quercitrin (**6**) (Song et al. 2008; Ishiguro et al. 1991), isoquercitrin (**7**) (Ishiguro et al. 1991; An et al. 2008), 1,5-di-*O*-caffeoylquinic acid (**8**) (An et al. 2008; Ela et al. 2012), and vicenin 1 (**9**) (Xie et al. 2003; Lin and Kong 2006) were identified by comparison with the spectroscopic data (^{1}H- and ^{13}C-NMR, and MS) from the literature.

AR activities of compounds **1–9** from *S. grandifolia*

Compounds **1**-**9** were assayed for AR inhibitory activity, using an assay that demonstrates the potential of a

Table 2 IC_{50} values of compounds **1–9** on AR inhibition

Compound	Concentration (μg/mL)	Inhibition[a] (%)	IC_{50}^{b} (μM)
1	10	96.0	1.45
	5	80.8	
	0.1	21.1	
2	10	74.8	8.34
	5	51.2	
	1	23.5	
3	10	60.1	14.66
	5	34.3	
	1	8.1	
4	10	21.6	–
5	10	50.5	22.83
	5	31.2	
	1	15.7	
6	10	97.7	0.34
	1	69.5	
	0.1	45.7	
7	10	87.2	0.32
	1	65.9	
	0.1	46.9	
8	10	95.4	0.08
	0.1	64.6	
	0.05	45.7	
9	10	24.9	–
TMG[c]	5	78.5	5.16
	1	59.0	
	0.5	32.2	

[a] Inhibition rate was calculated as a percentage with respect to the control value

[b] IC_{50} value was calculated from least-squares regression analysis of the plot of the logarithm of three graded concentrations versus % inhibition

[c] TMG was used as a positive control

compound for the prevention of the complications of diabetes. To evaluate rat lens AR inhibitory activity, inhibitory percentage and IC_{50} values were calculated. The flavonoid and phenol constituents showed strong AR inhibitory activity (Collins and Corder 1977; de la Fuente and Manzanaro 2003; Kawanishi et al. 2003; Mok and Lee 2013) with the exception of compounds **4** and **9**. Vitexin (**1**), genkwanin-5-*O*-glucoside (**2**), quercitrin (**6**), isoquercitrin (**7**), and 1,5-di-*O*-caffeoylquinic acid (**8**) all demonstrated >70 % inhibitory activity against AR. In particular, vitexin (**1**), quercitrin (**6**), and 1,5-di-*O*-caffeoylquinic acid (**8**) produced >90 % inhibition. Compounds having more than 50 % inhibitory activity were tested for AR inhibitory activity at three graded concentrations (Table 2).

Previous studies have demonstrated the following relationships between the structure and inhibitory activity of flavonoids: (1) flavonoid mono glycosides (compounds **1**, **2**, and **7**) are more active than flavonoid diglycosides (compounds **4** and **9**) (Kawanishi et al. 2003); (2) hydroxyl group substituted flavonoids (compounds **1** and **7**) are more active than methoxyl groups (compound **2**) (Kawanishi et al. 2003); (3) flavones and flavonols having a caffeic acid moiety (ABX type of flavonoid B-ring, compounds **6** and **7**) show stronger activity than the A_2B_2 type flavonoid B-ring (compounds **1–5** and **9**) (Kim et al. 2011a, b). The inhibitory activities of the eight flavonoids isolated from *S. grandifolia* against AR were similar to those previously reported. In these results, quercitrin (**6**) and isoquercitrin (**7**) showed high inhibitory activity (with IC_{50} values of 0.16 and 0.32 μM, respectively), approximately 1.5–3 times more potent than TMG. We previously reported that luteolin, luteolin 7-*O*-glucoside, quercetin, isorhamnetin 3-*O*-glucoside, and protocatechualdehyde have strong AR inhibitory activities among the single compounds isolated from natural products (Kim et al. 2011a, b; Mok et al. 2011; Lee et al. 2005a, b). In particular, 1,5-di-*O*-caffeoylquinic acid (**8**) exhibited the highest activity (IC_{50} = 0.08 μM), 6.5 times more potent than TMG. 1,5-di-*O*-caffeoylquinic acid (**8**) is composed of caffeoyl acid units. In previous studies, caffeic acid had no inhibitory activity against AR, but the caffeoyl derivatives 3,5-di-*O*-caffeoylquinic acid from *Ipomoea batatas* (Kawanishi et al. 2003) and 4,5-di-*O*-caffeoylquinic acid from *Artemisia montana* and *A. dracunculus* (Logendra et al. 2006; Jung et al. 2011) have strong inhibitory activities against AR (IC_{50} values, 0.46 and 7.26 μM, respectively). Caffeoyl groups bound to quinic acid are important for biological activities (Miyamae et al. 2011; Saleem et al. 2004).

This is the first report on the isolation of compounds **1–9** from *S. grandifolia*. Quercitrin (**6**), isoquercitrin (**7**), and 1,5-di-*O*-caffeoylquinic acid (**8**) showed high AR inhibitory activities, which may demonstrate the potential therapeutic applications of Korean edible mountain vegetables. *S. grandifolia* as mountain vegetables is gradually increasing as people become more concerned about their health and well-beings. In previous papers, compounds **6**, **7**, and **8** had no cytotoxicity and showed high AR inhibitory activities (Babujanarthanam et al. 2010; Park et al. 2009; Jung et al. 2011; Mok and Lee 2013). Our research demonstrated that *S. grandifolia* as Korean edible mountain vegetables containing quercitrin (**6**), isoquercitrin (**7**), and 1,5-di-*O*-caffeoylquinic acid (**8**) is clearly a potential candidate as a therapeutic or preventive agent for the treatment of diabetic complications.

Acknowledgments This work was supported by grants from Scientific Research of Korea National Arboretum (KNA1-2-13, 11-5), Cooperative Research Program for Agriculture Science & Technology Development (Project No. PJ010156022014), Rural Development Administration, and iPET (Korea Institute of Planning and Evaluation

for Technology in Food, Agriculture, Forestry, and Fisheries), Ministry of Agriculture, Food, and Rural Affairs, Republic of Korea. We thank the National Center for Inter-University Research Facilities (Seoul National University, Republic of Korea) for the NMR and MS measurements.

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