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Horticulture, Environment, and Biotechnology

ISSN 2211-3452
Volume 59
Number 1

Hortic. Environ. Biotechnol. (2018)
59:131-137
DOI 10.1007/s13580-018-0014-2

Springer

Horticulture, Environment, and Biotechnology (2018) 59:131–137
https://doi.org/10.1007/s13580-018-0014-2

RESEARCH REPORT

Determination of flavonoids in *Acer okamotoanum* and their aldose reductase inhibitory activities

Jaemin Lee[1] · Dong-Gu Lee[1] · Joyce P. Rodriguez[1] · Jun Yeon Park[2] · Eun Ju Cho[3] · Sonia D. Jacinto[4] · Sanghyun Lee[1]

Received: 11 August 2016 / Revised: 20 April 2017 / Accepted: 13 July 2017 / Published online: 14 February 2018

Abstract
Plants in the genus *Acer* include medicinal plants and deciduous tree species in which several bioactive compounds have been isolated. In this study, flavonoids were isolated from the aerial parts of *Acer okamotoanum* by open column chromatography and identified by spectroscopic analysis as afzelin, quercitrin, and isoquercitrin. Among these flavonoids, quercitrin and isoquercitrin exhibited potent aldose reductase inhibitory activity (IC_{50} value of 0.40 and 0.63 μM, respectively). Almost all studied tissues of *Acer* spp. contained high amounts of quercitrin. The leaf of *A. mono* had the highest amount of quercitrin (61.90 μg g^{-1}). Our results demonstrated that *Acer* species contain high concentrations of flavonoids with promising aldose reductase inhibitory activity that could be utilized to develop novel therapeutics for diabetic disorders.

Keywords Aceraceae · Bioassay · Constituent · Flavonoid

1 Introduction

The genus *Acer*, which belongs to the Aceraceae family, includes medicinal plants and deciduous tree species that are distributed across China, Japan, and Korea. Three species and several varieties of the genus *Acer* are found in Korea, namely, *A. mono, A. mono* var. *rulbripes, A. mono* var. *savatieri, A. mono* var. *horizontale, A. mono* var. *ambiguum, A. mono* f. *dissectum, A. mono* f. *connivens, A. truncatum,* and *A. okamotoanum* (Lee 1982). Particularly, *A. okamotoanum* is endemic in Ulleung Island, Korea (Takayama et al. 2013). Phytochemical and biological studies on *A. okamotoanum* have shown that it exhibits activities against HIV-1 integrase and have demonstrated to improve cognition and memory (Kim et al. 1998; Moon and Kwon 2004; Jin et al. 2007; Choi et al. 2017; Park et al. 2016). Moreover, cleomiscosins A and C from the plant have antioxidant activity and are effective at inhibiting low-density lipoprotein oxidation (Wen et al. 2007).

Aldose reductase (AR) is an essential enzyme of the polyol pathway which plays a significant role in the development of diabetic complications (Mok et al. 2012). It is a cytoplasmic enzyme present in various cell types and distributed in organs commonly afflicted with diabetic disorders (e.g., eyes, kidney, and brain). Moreover, it has been observed that AR activity during hyperglycemic conditions, a characteristic symptom of diabetes, is drastically increased. Thus, showing the role of AR in the pathogenesis of diabetic complications. Numerous studies on AR have provided evidence that the accumulation of the products of the polyol pathway such as sorbitol and reactive oxygen species (ROS) result to osmotic and oxidative stress, respectively. This results to detrimental effects in affected cells which ultimately leads to the development and progression of diabetic complications (Ohta et al. 1996; Bhandari et al. 2016). Due to this important role AR plays, inhibition of the enzyme has become an attractive strategy for the prevention and management of the complications associated with diabetic hyperglycemia. Many ARIs have been developed to prevent the development of diabetic complications such as zopolrestat, tolerestat, and sorbinil, which bind to active site of AR, thus inhibiting its activity (Constantino et al. 1999; Hotta et al. 2006; Sun et al. 2006; Drel et al. 2008;

✉ Sanghyun Lee
slee@cau.ac.kr

[1] Department of Integrative Plant Science, Chung-Ang University, Anseong 17546, Republic of Korea

[2] College of Korean Medicine, Gachon University, Seongnam 13120, Republic of Korea

[3] Department of Food Science and Nutrition, Pusan National University, Busan 46241, Republic of Korea

[4] Institute of Biology, University of the Philippines, Diliman, 1101 Quezon, Philippines

Matsumoto et al. 2008). Also, evaluating natural sources for ARIs may aid in the development of more effective agents for preventing diabetic complications (De la Fuente and Manzanaro 2003). Particularly, flavonoids are a group of naturally occurring compounds known to exhibit AR inhibitory effects. Accordingly, the chemical constituents of *A. okamotoanum* and their biological activities have not been thoroughly investigated to date.

Hence, the goal of this study was to isolate and identify flavonoid compounds from *A. okamotoanum* by ^{1}H- and ^{13}C-nuclear magnetic resonance (NMR) and mass spectrometry (MS). This study also aimed to evaluate the inhibitory effects of the compounds purified from *A. okamotoanum* on AR and to determine their respective contents in the plant by high performance liquid chromatography/ultra violet (HPLC/UV) analysis.

2 Materials and methods

2.1 Plant materials

Acer okamotoanum plants were collected at Ulleung Island by the Korea National Arboretum. The different tissues (leaf, stem, bark, heartwood, and roots) were extracted from *A. okamotoanum* with MeOH in our lab and the other samples (see Table 1) were purchased from Korea Research Institute Bioscience and Biotechnology, totaling thirteen samples.

2.2 Instruments and chemicals

Fast atom bombardment-mass spectrometry (FAB-MS) was performed with a JEOL JMS-AX505WA (Japan) mass spectrometer. ^{1}H- and ^{13}C-NMR spectra were measured with a Bruker AVANCE 500 NMR (Germany) spectrometer, and the absorbance at UV wavelengths (340 nm) was measured with an Optizen 2120 UV/Vis spectrophotometer. MeOH, *n*-hexane, dichloromethane (CH_2Cl_2), ethyl acetate (EtOAc), and *n*-butanol (*n*-BuOH) were purchased from Samchun Pure Chemicals Co., Ltd. (Pyeongtaek, Republic of Korea). Solvents DL-glyceraldehyde, β-NADPH, sodium phosphate buffer, potassium phosphate buffer, and dimethylsulfoxide (DMSO) were purchased from Sigma-Aldrich Chemical Co., Ltd. (St. Louis, MO, USA).

Table 1 Samples used for quantitative analysis

Species	Tissue	Abbreviation of samples
A. okamotoanum	Leaf	AOL
	Stem and bark	AOS
	Root	AOR
A. mono	Leaf	AML
	Bark	AMB
	Heartwood	AMH
A. truncatum	Leaf	ATL
	Leaf and stem	ATM
	Stem	ATS
A. pictum var. *mono*	Leaf	APL
	Leaf and stem	APM
	Stem	APS
A. pictum var. *truncatum*	Bark	ATB

2.3 Extraction and fractionation methods

Aerial parts of *A. okamotoanum* (995.4 g) were shade dried, pulverized, and extracted with 4 L of MeOH for 3 h under a reflux system at 65–75 °C. The extraction procedure was repeated for 8 times. The resulting extract was filtered and evaporated in vacuum to obtain the dried MeOH extract (176.1 g). This extract was suspended in distilled water and partitioned successively with *n*-hexane, CH_2Cl_2, EtOAc, and *n*-BuOH. Each fraction of *n*-hexane, CH_2Cl_2, EtOAc, and *n*-BuOH was evaporated under reduced pressure to yield 27.6, 5.8, 35.0, and 7.4 g of residues, respectively.

2.4 Isolation of phytochemicals from *A. okamotoanum*

The bioactive EtOAc fraction (30 g) was subjected to silica gel column chromatography (6 × 80 cm, No. 7734) using a gradient system of $CHCl_3$/MeOH (10:0–0:10 v/v) to yield

Table 2 AR inhibitory activity (IC_{50}) of the MeOH extract and fractions from *A. okamotoanum* on rat lens AR

Sample	Concentration (μg mL^{-1})	AR inhibition[a] (%)	IC_{50}^{b} (μg mL^{-1})
MeOH extract	10	78.43	4.12
	1	16.98	
	0.1	12.07	
n-Hexane fraction	10	64.37	–
CH_2Cl_2 fraction	10	36.27	–
EtOAc fraction	10	92.81	0.34
	1	65.66	
	0.1	19.62	
n-BuOH fraction	10	33.98	–
TMG[c]	10	83.28	0.28
	1	62.21	
	0.1	40.13	

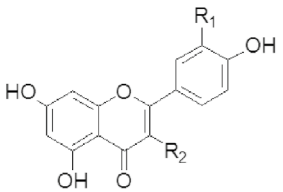
[a]Inhibition rate was calculated as a percentage of the control value

[b]IC_{50} values calculated from the least-squares regression line of the logarithmic concentrations plotted against the residual activity

[c]TMG was used as a positive control

Table 3 ^{1}H- and ^{13}C-NMR spectral data for compounds **1**–**3** (DMSO-d_6) from *A.okamotoanum*

Position	Afzelin (**1**)		Quercitrin (**2**)		Isoquercitrin (**3**)	
	δ_H	δ_C	δ_H	δ_C	δ_H	δ_C
2		157.1		157.3		156.3
3		134.2		134.2		133.5
4		177.6		177.7		177.5
5		161.2		161.3		161.2
6	6.20 (d, 2)	98.7	6.18 (d, 1.5)	98.7	6.19 (d, 2)	98.6
7		164.2		164.2		164.1
8	6.40 (d, 2)	93.7	6.36 (d, 1.5)	93.6	6.39 (d, 2)	93.5
9		156.4		156.4		156.3
10		104.0		104.1		103.9
1′		120.5		121.1		121.9
2′	7.75 (d, 7.0)	130.5	7.29 (d, 2.0)	115.6	7.52 (d, 2.0)	115.2
3′	6.91 (d, 7.0)	115.3		145.2		144.8
4′		159.9		148.4		148.5
5′	6.91 (d, 7.0)	115.3	6.85 (d, 8.0)	115.6	6.80 (d, 8.5)	115.9
6′	7.75 (d, 7.0)	130.5	7.24 (dd, 8.0, 2.0)	121.1	7.66 (dd, 8.5, 2.0)	121.1
Glc-1	5.28 (d, 2.0)	101.7	5.25 (d, 1.5)	101.8	5.37 (d, 7.5)	101.8
Glc-2		70.0		70.0		71.2
Glc-3		70.3		70.3		73.2
Glc-4		71.1		71.2		67.9
Glc-5		70.5		70.6		75.8
Glc-6	0.78 (d, 6.0)	17.4	0.81 (d, 6.0)	17.5		60.1
5-OH	12.62 (s)	–	12.65 (s)	–	12.63 (s)	–



Compound	R_1	R_2
Afzelin (**1**)	H	*O*-Rham
Quercitrin (**2**)	OH	*O*-Rham
Isoquercitrin (**3**)	OH	*O*-Glc

Fig. 1 Chemical structures of compounds **1**–**3**

Table 4 AR inhibitory activity (IC_{50}) of flavonoids from *A. okamotoanum* on rat lens AR

Compound	Concentration (μg mL^{-1})	AR inhibition[a] (%)	IC_{50}^{b} (μg mL^{-1})
Afzelin (**1**)	10	85.62	1.13 (2.61 μM)
	1	51.51	
	0.1	6.69	
Quercitrin (**2**)	10	89.54	0.31 (0.40 μM)
	1	81.13	
	0.1	26.79	
Isoquercitrin (**3**)	10	91.64	0.29 (0.63 μM)
	1	80.94	
	0.1	28.43	
TMG[c]	10	83.28	0.28 (1.52 μM)
	1	62.20	
	0.1	40.13	

[a]Inhibition rate was calculated as a percentage of the control value

[b]IC_{50} values calculated from the least-squares regression line of the logarithmic concentrations plotted against the residual activity

[c]TMG was used as a positive control

12 fractions. Fraction 9 was subjected to LiChroprep column chromatography (Merck, Damstadt, Germany) with a gradient of MeOH/H_2O (5:5–10:0 v/v) to obtain 9 sub-fractions. Among them, sub-fraction 8 was repeatedly chromatographed on a Sephadex LH-20 column eluted with a MeOH/water gradient (5:5–10:0 v/v) to obtain 9 additional sub-fractions. Sub-fraction 5 was recrystallized with MeOH to yield afzelin (compound **1**). Fraction 10 was recrystallized with MeOH to yield quercitrin (compound **2**). Fraction 11 was rechromatographed on a Sephadex LH-20 column eluted with a MeOH/water gradient (5:5–10:0 v/v) to obtain

20 sub-fractions. Among these 20 sub-fractions, sub-fraction 15 yielded isoquercitrin (compound **3**).

Compound **1**: yellow amorphous powder; FAB-MS: *m/z* 433 $[M + H]^+$; purity 96%
Compound **2**: yellow amorphous powder; FAB-MS: *m/z* 449 $[M + H]^+$; purity 97%
Compound **3**: yellow amorphous powder; FAB-MS: *m/z* 465 $[M + H]^+$; purity 99%

2.5 Measurement of AR activity

Rat lenses removed from Sprague–Dawley rats (weighing 250–280 g) were preserved by freezing until use. The lenses were homogenized and centrifuged at 10,000 rpm (4 °C, 20 min) and the supernatant was used as a source of AR. AR activity (EC 1.1.1.21) was measured according to a previous method (Sato and Kador 1990). Tetramethylene glutaric acid (TMG), which is an ARI, was used as a positive control.

Table 5 Quantities of compounds **1**–**3** in each part of *Acer* spp.

Sample	Content (μg g^{-1})			
	Afzelin (**1**)	Quercitrin (**2**)	Isoquercitrin (**3**)	Total
AOL	2.66 ± 0.06	48.13 ± 0.19	5.56 ± 0.06	56.35 ± 0.31
AOS	–	0.09 ± 0.00	0.05 ± 0.00	0.14 ± 0.00
AOR	–	0.04 ± 0.01	0.23 ± 0.01	0.27 ± 0.02
AML	4.07 ± 1.17	61.90 ± 0.11	7.30 ± 0.10	73.27 ± 1.38
AMB	–	–	–	–
AMH	0.40 ± 0.15	0.25 ± 0.00	0.18 ± 0.02	0.83 ± 0.17
ATL	4.81 ± 0.11	14.23 ± 0.14	0.39 ± 0.00	19.43 ± 0.25
ATM	2.99 ± 0.04	51.51 ± 0.06	0.72 ± 0.02	55.22 ± 0.12
ATS	0.07 ± 0.01	0.60 ± 0.01	0.19 ± 0.01	0.86 ± 0.03
APL	4.34 ± 0.17	36.86 ± 0.37	3.79 ± 0.08	44.99 ± 0.62
APM	1.72 ± 0.17	34.44 ± 0.36	1.62 ± 0.04	37.78 ± 0.57
APS	0.08 ± 0.00	0.30 ± 0.01	0.50 ± 0.02	0.88 ± 0.03
ATB	–	0.03 ± 0.00	–	0.03 ± 0.00

Data are represented as the mean ± S.D. (n = 3) in μg g^{-1} of the dried samples

2.6 Sample preparation for HPLC

To analyze compounds **1**–**3** by HPLC in the thirteen samples, samples were prepared by dissolving 20 mg of the test extracts with 1 mL MeOH. The solutions used for HPLC were filtered through a 0.45 μm syringe filter.

2.7 Quantitative analysis of the flavonoids from *A. okamotoanum* tissues

HPLC analysis of compounds **1**–**3** was conducted with Waters Spherisorb and INNO C18 column (4.6 × 250 mm, 5 μm) (Seongnam, Republic of Korea). A mobile phase containing 0.5% acetic acid (sovent A) and MeOH (sovent B) were used for gradient HPLC. Chromatographic separation was performed with an initial gradient of 70:30 (A: B), followed by a gradient of 60: 40 for 10 min, 63:37 for 5 min at 0.8 mL min^{-1}; and 0:100 for 25 min. The 0:100 gradient was maintained for another 5 min, which is then followed by a 70: 30 solvent ratios maintained for 5 min. The flow rate was adjusted to 1 mL min^{-1} and UV detection was set at 330 nm.

2.8 Limits of detection and quantification

Validation of the HPLC method for compounds **1**–**3** was conducted by determining the limit of detection and limit of quantification (LOD and LOQ, respectively). The method linearity was established following triplicate injections (range 0.1–1000 μg mL^{-1}). The values of LOD and LOQ were determined according to a previous method (Mok and Lee 2013).

2.9 Calibration curves

Standard stock solutions (0.1–1000 μg mL^{-1}) of compounds **1**–**3** were prepared in MeOH solution. The contents of compounds **1**–**3** in the samples were measured using the corresponding calibration curves. The calibration curve of compounds **1**–**3** was calculated by the peak area (Y), concentration (X, mg mL^{-1}), and mean values (n = 3) ± standard deviation (SD).

Table 6 LOD and LOQ values of compounds **1**–**3**

Compound	Calibration equation[a]	r^{2b}	Linear range (mg mL^{-1})	LOD (mg mL^{-1})	LOQ (mg mL^{-1})
Afzelin (**1**)	Y = 428405X + 46.304	0.9992	0.1–1.000	0.001	0.002
Quercitrin (**2**)	Y = 233887X + 36.195	0.9983	0.1–1.000	0.001	0.004
Isoquercitrin (**3**)	Y = 286221X + 43.658	0.9984	0.1–1.000	0.001	0.003

[a]Y = peak area, X = concentration of standard (mg mL^{-1})
[b]r^2 = correlation coefficient for three data points in the calibration curve

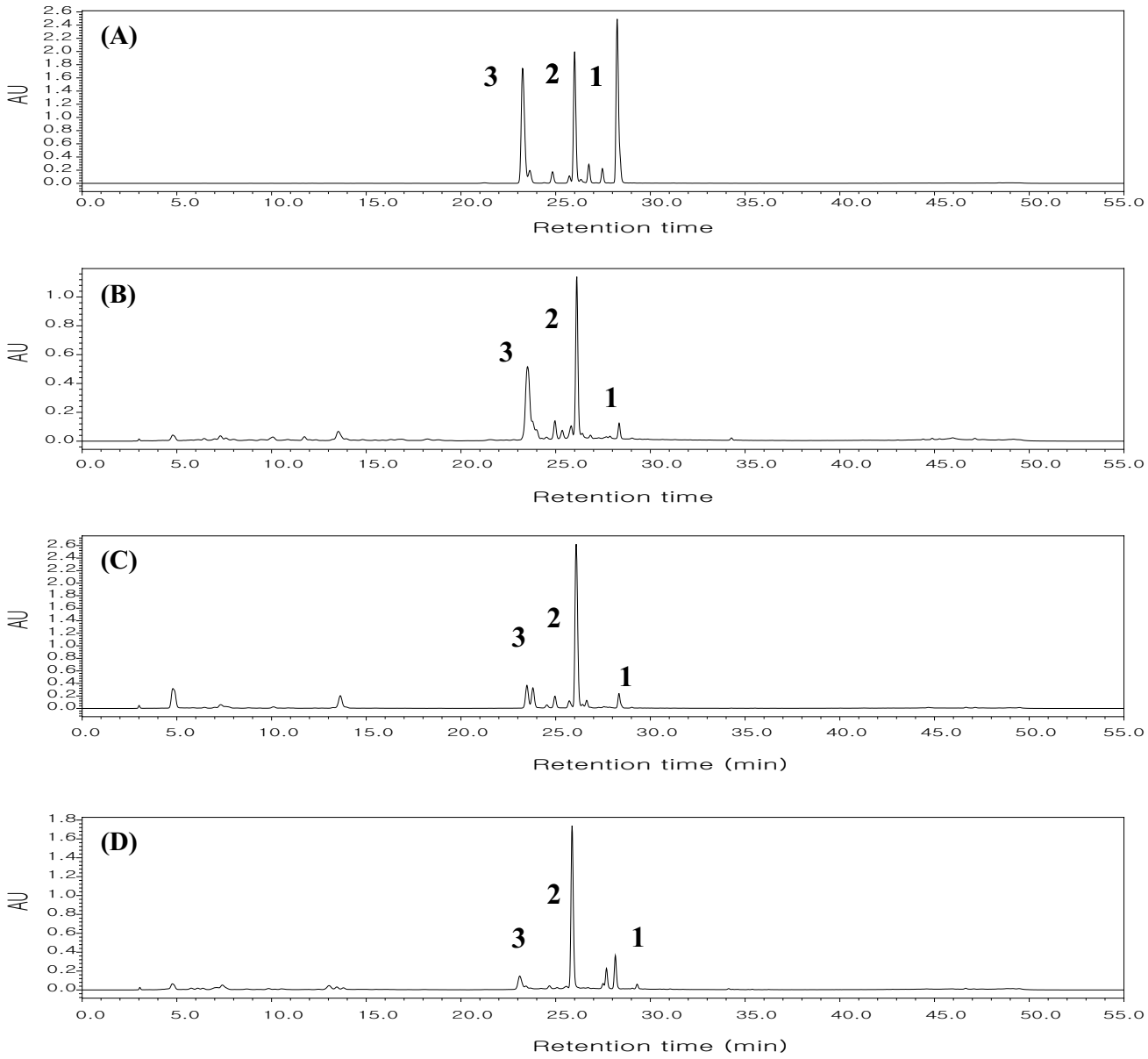


Fig. 2 HPLC chromatograms of compounds **1**–**3** (**a**), AOL (**b**), AML (**c**), and APL (**d**)

3 Results and discussion

3.1 AR inhibitory activity of the *A. okamotoanum* extracts

MeOH extracts and fractions of the tissues of *A. okamotoanum* were tested for their AR inhibitory activity. The EtOAc fraction showed potent inhibition against rat lens AR (IC_{50} value 0.34 μg mL^{-1}) (Table 2). In previous studies, *A. okamotoanum* showed HIV-1 integrase inhibitory activity, anti-complement activity, and cytotoxicity activities against four cancer cell lines (Kim et al. 1998; Jin et al. 2006, 2007). In our study, the EtOAc fraction from aerial parts of *A. okamotoanum* showed AR inhibitory activity.

3.2 Identification of compounds 1–3 from *A. okamotoanum* and their AR inhibitory activity

Chromatographic separation of the EtOAc fraction of *A. okamotoanum* led to the isolation of compounds **1**–**3**. These compounds were identified as afzelin (**1**), quercitrin (**2**), and isoquercitrin (**3**) by comparing the ^{1}H-NMR, ^{13}C-NMR, and MS data with previous literatures (Table 3) (Miyazaki et al. 1991; Hasan et al. 2006; Bolingon et al. 2009; Chang et al. 2009). Structural data of the compounds are shown in Fig. 1.

Compounds **1**–**3** have previously been isolated from *A. cissifolium* (Chang et al. 2009). However, our study is the first to isolate these compounds from *A. okamotoanum*. Afzelin demonstrates anti-bacterial effects (Varma et al. 1975; Lee et al. 2014). Quercitrin has anti-melanogenic effects (Park et al. 2014; Hong et al. 2013). Isoquercitrin shows anti-hypertensive and anti-proliferative effects (Amado et al. 2009; Gasparotto Junior et al. 2011). Compounds **1**–**3** were tested for their AR inhibitory activity. The AR inhibitory activities of quercitrin and isoquercitrin (0.40 and 0.63 μM, respectively) were higher than the positive control TMG (1.52 μM) (Table 4). The results are consistent with the numerous publications that have described the inhibitory effects of flavonoids against AR (Oliveira et al. 1997; Jung et al. 2009; Kim et al. 2011; Reddy et al. 2011; Kim et al. 2015). Quercitrin and isoquercitrin, which have dihydroxy structures in the B-ring, showed better inhibition than afzelin which has a mono-hydroxyl structure. This result demonstrated that the AR inhibitory activity may depend on the number of hydroxyl groups (Okuda et al. 1984). The catechol moiety at the B-ring promotes better AR inhibitory activity (Oliveira et al. 1997; Abou-zaid et al. 2008), and the three compounds had a catechol moiety group in their structure.

3.3 Quantitative analysis, LOD, and LOQ of compounds 1–3 in *A. okamotoanum*

HPLC/UV was conducted to determine the content of compounds **1**–**3** isolated from *A. okamotoanum*. The retention times of compounds **1**–**3** were 28.38, 23.39, and 26.06 min, respectively. The afzelin concentrations in the ATL, APL, and AML samples were 4.81, 4.34, and 4.07 μg g^{-1} extract, respectively. The quercitrin concentrations in the AML, AOL, and APL samples were 61.90, 51.51, and 48.13 μg g^{-1} extract, respectively. The isoquercitrin concentrations in the AML, ATM, and AOL samples were 7.30, 5.56, and 3.79 μg g^{-1} extract, respectively. The AML sample contained high concentrations of all three compounds (73.27 μg g^{-1}) (Table 5 and Fig. 2) (Li et al. 2008), especially quercitrin. Other studies have shown that *A. mono* contains quercitrin and isoquercitrin (Park and Kim 1995). The flavonoids in the *A. okamotoanum* extracts were quantified using a calibration curve. Quercitrin and isoquercitrin in rat plasma, seasonal variation of flavonoids in *Cedrela sinensis* (Li et al. 2008), and flavonoid content in Canadian goldenrod (*Solidago canadensis*) were determined by HPLC (Apati et al. 2002). The LOD and LOQ of compounds **1**–**3** were 0.001–0.001 and 0.002–0.004 mg mL^{-1}, respectively (Table 6).

Our results showed that quercitrin and isoquercitrin had potent AR inhibitory activities. Quercitrin is a major flavonoid and is expected to play a significant role in the management of diabetic complications. These results could be used as a guideline for the analysis of flavonoids in *Acer* spp. Although common flavonoids have been analyzed, this is the first report on the quantification of flavonoids in *Acer* spp. Moreover, further studies are needed on the potential use of the three flavonoids present in *A. okamotoanum* as raw materials for food supplements and anti-diabetic drugs.

Acknowledgements This work was supported by the Chung-Ang University Research Grants in 2017 and Basic Science Research Program through the National Research Foundation of Korea (NRF) funded by the Ministry of Education (2015R1D1A1A01058868).

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