



Inhibitory activity of methanol extracts from different colored flowers on aldose reductase and HPLC-UV analysis of quercetin

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Abstract

The methanol extracts of flowers obtained from 67 plant species were screened for their inhibitory activity on aldose reductase (AR). *Alnus japonica*, *Aster spathulifolius*, *Chionanthus retusus*, *Morus bombycis*, *Crysanthemum boreale*, *Persicaria tinctoria*, *Platycarya strobilacea*, and *Serratula coronata* var. *insularis* exhibited potent aldose reductase inhibitory (ARI) activity. HPLC-UV analysis of quercetin, an AR inhibitory flavonoid, was performed on extracts showing strong ARI activity. Quercetin was detected in *C. retusus*, *C. boreale*, *P. tinctoria*, and *S. coronata* var. *insularis* at concentrations of 1.33, 1.56, 0.82, and 3.37 mg g⁻¹ extract, respectively, indicating that quercetin contributed to the ARI activity of these extracts. In the samples in which quercetin was absent, other compounds may be responsible for their potent ARI activity. These results serve as a basis for further studies regarding the bioactive components responsible for the inhibitory effects of various flower extracts on AR activity.

Keywords Biological activity · Native plant · Plant flower · Flavonoid · Standardization

1 Introduction

Aldose reductase (AR) is an oxidoreductase that catalyzes the NADPH-dependent reduction of various aldehydes and aldoses. It is the first enzyme of the polyol pathway, which is responsible for the conversion of glucose to sorbitol (Tang et al. 2012). In hyperglycemic conditions, an increased flux of non-phosphorylated glucose into the polyol pathway results in heightened levels of reactive oxygen species and an imbalance in NADH/NAD⁺, which ultimately results in oxidative stress within cells (Lorenzi 2007). The cellular stress generated from the polyol pathway during such conditions is linked to the pathogenesis of complications associated with diabetic hyperglycemia such as neuropathy, retinopathy, and nephropathy (Dunlop 2000). The association

between diabetes-induced tissue damage and the polyol pathway is further supported by the observation that the activity of the enzymes of the polyol pathway is increased under high glucose conditions and by their presence in most tissues and organs that are susceptible to diabetic complications such as the lenses, kidneys, and neurons (Brownlee 2004). Moreover, inhibition of AR, a rate-limiting enzyme of the polyol pathway, has been shown to delay and prevent the onset of tissue-injury in hyperglycemic animal models, indicating that this pathway plays a role in the etiology of diabetic diseases (Cheung et al. 2005). Thus, inhibition of AR is an attractive target for drug design to mitigate diabetic complications.

Many studies have reported on the potent inhibitory properties of various phytochemicals on AR including quercetin, quercitrin, epicatechin gallate, isoquercitrin, and rutin (Grewal et al. 2016). The aim of this study is to screen the AR inhibitory (ARI) activity of different flowers collected in Korea and to quantify the amount of quercetin in the extracts showing potent ARI effects. The results of this study provide preliminary information as to which plant extracts show promising ARI activity.

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Table 1 IC₅₀ of white flower extracts on rat lens AR

Sample	Concentration (µg mL ⁻¹)	Inhibition ^z (%)	IC ₅₀ ^y (µg mL ⁻¹)
<i>Angelica fallax</i> ^w	10	74.16	0.77
	1	52.63	
	0.1	46.41	
<i>Aruncus dioicus</i> var. <i>kamtschaticus</i> ^w	10	77.99	3.46
	1	44.98	
	0.1	30.14	
<i>Aster scaber</i> ^w	10	78.47	2.94
	1	44.98	
	0.1	35.89	
<i>Castanea crenata</i> ^w	10	88.00	0.48
	1	67.20	
	0.1	24.80	
<i>Chionanthus retusus</i> ^y	10	85.29	0.25
	1	74.26	
	0.1	35.51	
<i>Crataegus maximowiczii</i> ^w	10	88.00	1.09
	1	51.20	
	0.1	4.80	
<i>Hydrangea paniculata</i> ^w	10	42.11	–
<i>Maianthemum dilatatum</i> ^w	10	43.06	–
<i>Magnolia kobus</i> ^y	10	25.50	–
<i>Meliosma myriantha</i> ^w	10	58.40	1.23
	1	52.00	
	0.1	36.60	
<i>Miscanthus sinensis</i> var. <i>purpurascens</i> ^w	10	36.36	–
<i>Morus bombycis</i> ^w	10	90.40	0.18
	1	59.81	
	0.1	47.85	
<i>Prunus padus</i> ^w	10	76.56	0.84
	1	53.59	
	0.1	44.98	
<i>P. serrulata</i> ^y	10	68.86	2.52
	1	35.33	
	0.1	10.78	
<i>P. serrulata</i> var. <i>spontanea</i> ^y	10	69.46	5.93
	1	28.74	
	0.1	19.43	
<i>Pyrus pyrifolia</i> ^y	10	80.88	0.46
	1	72.06	
	0.1	25.37	
<i>Rhododendron schlippenbachii</i> f. <i>albiflorum</i> ^y	10	35.93	–
<i>Robinia pseudoacacia</i> ^w	10	35.41	–
<i>Sorbus commixta</i> ^w	10	67.94	0.72
	1	58.85	
	0.1	31.00	
<i>Spiraea blumei</i> ^w	10	79.20	0.73
	1	60.00	
	0.1	22.40	

Table 1 (continued)

Sample	Concentration ($\mu\text{g mL}^{-1}$)	Inhibition ^z (%)	IC ₅₀ ^y ($\mu\text{g mL}^{-1}$)
<i>S. prunifolia</i> var. <i>simpliciflora</i> ^v	10	71.81	0.93
	1	56.38	
	0.1	24.16	
<i>Syringa vulgaris</i> ^v	1	51.01	–
<i>Tulipa gesneriana</i> ^v	10	48.00	–
TMG ^x	10	99.62	0.17
	1	67.31	
	0.1	45.38	

^zInhibition was calculated as a percentage of the control value

^yIC₅₀ values were calculated from the least-squares regression line of the logarithmic concentrations plotted against the residual activity

^xTMG was used as a positive control

^wMeOH extracts were purchased from KRIBB

^vFlowers were collected from field

2 Materials and methods

2.1 Plant materials and animal specimens

Flowers from 67 plant species were used in this study. The samples were either obtained from the field and extracted with methanol (MeOH) or purchased as MeOH extracts from the Korea Research Institute of Bioscience and Biotechnology (KRIBB), Korea (Tables 1, 2, 3, 4, 5, 6). Flowers were collected in Korea during the spring season. Flowers belonging to the same species but having different colors were considered as separate samples. Prior to extraction, the flowers were dried in the shade and voucher specimens were deposited at the herbarium of the Department of Integrative Plant Science, Chung-Ang University, Korea. Seven-week-old Sprague-Dawley rats weighing 210–230 g were acquired from Koatech, Korea.

2.2 Chemicals and apparatuses

Sodium buffer, MeOH, and potassium buffer were obtained from Samchun Pure Chemical Co. (Pyeongtaek, Korea). Dimethyl sulfoxide (DMSO), 3,3'-tetramethyleneglutaric acid (TMG), DL-glyceraldehyde, and β -nicotinamide dinucleotide phosphate (NADPH) were purchased from Sigma Aldrich Chemical (St. Louis, USA). An EYELA rotary evaporator system (Japan) was used for evaporation *in vacuo*. An Allegra X-30R refrigerated benchtop centrifuge (Beckman Coulter™, MD, USA) and an Optizen 2120 UV spectrophotometer (Mecasys Co., Daejeon, Korea) were used for the ARI assay.

2.3 Sample preparation for the ARI assay

Six grams of dried flowers were extracted with 300 mL of methanol at 80 °C for 3 h. The resulting extracts were filtered to remove debris and evaporated to dryness under reduced pressure. The MeOH extracts were tested for their ARI activity. Samples were prepared for the assay by dissolving 1 mg of the flower extracts in 1 mL DMSO.

2.4 Preparation of AR from rat lenses

AR was prepared from rat lenses following a previously described protocol (Hayman and Kinoshita 1965). Lenses from healthy Sprague-Dawley rats were resected and homogenized in 0.1 M sodium buffer (pH 6.2), to which 0.5 mL buffer was added for every lens used. The homogenate was centrifuged at 10,000 rpm at 4 °C for 20 min, and the resulting supernatant was collected and used as the source of AR in the ARI activity assay.

2.5 Measurement of AR inhibitory activity

The ARI activity of the flower extracts was determined by spectrophotometrically measuring the decrease in NADPH absorbance at 340 nm for a period of 4 min, using DL-glyceraldehyde as a substrate for AR. The total volume of the assay solution was 1 mL and it comprised the rat lens AR, plant extract dissolved in DMSO, 25 mM DL-glyceraldehyde, 1.6 mM NADPH, 100 mM sodium buffer and 100 mM potassium phosphate buffer (pH 7.0). TMG was used as

Table 2 IC₅₀ of yellow flower extracts on rat lens AR

Sample	Concentration (µg mL ⁻¹)	Inhibition ^z (%)	IC ₅₀ ^y (µg mL ⁻¹)
<i>Alnus firma</i> ^w	10	33.97	–
<i>Aristolochia manshuriensis</i> ^w	10	44.98	–
<i>Brassica napus</i> ^y	10	44.9	–
<i>Chelidonium majus</i> var. <i>asiaticum</i> ^y	10	12.08	–
<i>Chrysanthemum boreale</i> ^w	10	87.20	0.25
	1	59.20	
	0.1	43.20	
<i>Cornus officinalis</i> ^y	10	88.97	0.28
	1	70.59	
	0.1	35.29	
<i>Edgeworthia papyrifera</i> ^w	10	77.60	0.53
	1	61.60	
	0.1	30.40	
<i>Farfugium japonicum</i> ^w	10	94.40	0.61
	1	57.60	
	0.1	21.60	
<i>Firmiana simplex</i> ^w	10	76.00	2.03
	1	36.00	
	0.1	5.60	
<i>Forsythia koreana</i> ^y	10	20.13	–
<i>Hibiscus hamabo</i> ^w	10	38.28	–
<i>Kerria japonica</i> ^y	10	73.90	0.5
	1	68.01	
	0.1	28.68	
<i>Lindera obtusiloba</i> ^w	10	83.73	0.95
	1	51.67	
	0.1	45.45	
<i>Platycarya strobilacea</i> ^w	10	95.22	0.18
	1	80.38	
	0.1	38.28	
<i>Salix graciliglans</i> ^w	10	40.80	–
<i>Taraxacum platycarpum</i> ^y	10	72.00	1.37
	1	54.40	
	0.1	11.20	
<i>Tulipa gesneriana</i> ^y	10	63.47	1.28
	1	47.20	
	0.1	34.69	
TMG ^x	10	99.62	0.17
	1	67.31	
	0.1	45.38	

Same as in Table 1

a positive control. The inhibitory activity of the samples was expressed as: (%) Inhibition = (normal enzyme activity – inhibited enzyme activity)/normal enzyme activity. The IC₅₀ values were determined from the least-squares regression line of the logarithmic concentrations plotted against residual activity.

2.6 Standard and sample preparation for HPLC-UV analysis

HPLC samples were prepared by dissolving 10–20 mg of the flower extracts in 1 mL MeOH. A standard stock solution of quercetin was prepared by dissolving 1 mg of quercetin in

Table 3 IC₅₀ of pink flower extracts on rat lens AR

Sample	Concentration (µg mL ⁻¹)	Inhibition ^z (%)	IC ₅₀ ^y (µg mL ⁻¹)
<i>Cosmos bipinnatus</i> ^w	10	44.50	–
<i>Eupatorium fortunei</i> ^w	10	55.02	4.11
	1	43.54	
	0.1	10.05	
<i>Lespedeza bicolor</i> ^w	10	48.80	–
	10	71.29	0.53
<i>Persicaria tinctoria</i> ^w	1	58.85	
	0.1	34.93	
	1	50.34	–
<i>Prunus serrulata</i> ^y	10	82.30	3.53
<i>Sedum spectabile</i> ^w	1	39.71	
	0.1	30.62	
	10	80.38	0.49
<i>Serratula coronata</i> var. <i>insularis</i> ^w	1	57.89	
	0.1	33.49	
	10	57.60	2.32
<i>Tulipa gesneriana</i> ^y	1	49.60	
	0.1	24.80	
	10	99.62	0.17
TMG ^x	1	67.31	
	0.1	45.38	

Same as in Table 1

1 mL MeOH. All samples were filtered through a 0.45-µm filter prior to use.

2.7 HPLC-UV analysis of quercetin in MeOH flower extracts

The extracts with the highest inhibitory effects on AR from each flower color category were analyzed for their quercetin content. An Agilent HPLC system was used for the analysis. Chromatographic separation was performed with a reverse-phase INNO C₁₈ (4.6 × 250 mm, 5 µm) column. A gradient elution of 0.5% acetic acid in water: acetonitrile (90:10 to 50:50 for 50 min) was followed. The flow rate and injection volume were 1 mL min⁻¹ and 10 µL, respectively. The UV detector was set at 270 nm.

2.8 Calibration curve

The working solutions used to construct a calibration curve were obtained by diluting the quercetin stock solution to the desired concentrations. The calibration curves were used to determine the quercetin content in the samples. Linearity was assessed based on the correlation coefficient (r^2).

3 Results and discussion

Diabetes is a metabolic disorder characterized by chronic hyperglycemia, and impaired fat, lipid, and carbohydrate metabolism. These attributes lead to various complications such as blindness, renal failure, and nerve damage, and thus, contribute to the overall morbidity of the disease. Studies have shown that the tissue damage caused by diabetic hyperglycemia is linked to four major mechanisms, namely, the increased flux of non-phosphorylated glucose to the polyol pathway, activation of the protein kinase C pathway, production of advanced glycation end-products, and increased activity of the hexosamine pathway (Brownlee 2001). The polyol pathway in particular has been widely studied because the inhibition of AR, a key enzyme of the pathway, prevents and sometimes reverts diabetic complications (Engerman et al. 1994; Brownlee 2004). To date, numerous AR inhibitors have been established including synthetic and naturally occurring compounds.

In this study, the inhibitory activity of MeOH extracts of various flowers on crude rat lens AR was evaluated. The samples were grouped according to their colors and the results are summarized in Tables 1, 2, 3, 4, 5 and 6. The results show that there is no apparent relationship between

Table 4 IC₅₀ of red flower extracts on rat lens AR

Sample	Concentration (µg mL ⁻¹)	Inhibition ^z (%)	IC ₅₀ ^y (µg mL ⁻¹)
<i>Camellia japonica</i> ^w	10	35.93	–
<i>Campsis grandiflora</i> ^w	10	66.03	0.63
	1	54.55	
	0.1	37.80	
<i>Celastrus orbiculatus</i> ^w	10	45.60	–
	10	81.60	0.21
<i>Chaenomeles lagenaria</i> ^v	1	65.60	
	0.1	42.40	
<i>Euscaphis japonica</i> ^w	10	96.00	0.81
	1	66.40	
	0.1	0.57	
<i>Paeonia suffruticosa</i> ^v	10	41.32	–
<i>Salix purpurea</i> var. <i>multinervis</i> ^w	10	71.77	0.44
	1	52.63	
	0.1	41.63	
<i>Tulipa gesneriana</i> ^v	10	76.40	0.29
	1	58.40	
	0.1	42.40	
<i>Zinnia elegans</i> ^v	10	89.26	0.57
	1	60.80	
	0.1	23.95	
TMG ^x	10	99.62	0.17
	1	67.31	
	0.1	45.38	

Same as in Table 1

Table 5 IC₅₀ of brown flower extracts on rat lens AR

Sample	Concentration (µg mL ⁻¹)	Inhibition ^z (%)	IC ₅₀ ^y (µg mL ⁻¹)
<i>Typha orientalis</i> ^w	10	37.32	–
<i>T. angustata</i> ^w	10	21.53	–
<i>Alnus japonica</i> ^w	10	88.00	0.18
	1	76.80	
	0.1	39.23	
<i>Carpinus laxiflora</i> ^w	10	94.00	0.33
	1	76.00	
	0.1	28.00	
TMG ^x	10	99.62	0.17
	1	67.31	
	0.1	45.38	

Same as in Table 1

flower color and ARI activity of the MeOH extracts from the flowers that we screened. However, we observed that purple and darker colored flowers tend to have lower inhibitory

activity against AR. Among the extracts tested, *A. japonica*, *M. bombycis*, and *P. strobilacea* showed the most potent ARI effects, all having an IC₅₀ value of 0.18 µg mL⁻¹. The potent ARI activity of these extracts can be attributed to the presence of bioactive compounds. *A. japonica* is abundant in diarylheptanoids, a class of compounds shown to exhibit ARI activity (Kuroyanagi et al. 2005). Diarylheptanoids, specifically gingerenones, isolated from *Zingiber officinale* have a high binding affinity towards AR (Antony and Vijayan 2015). This finding suggests that diarylheptanoids present in *A. japonica* might also have a high binding affinity towards AR, providing a possible explanation for its inhibitory effect on AR. Recent studies have shown that *Morus* spp. contain many bioactive compounds including flavonoids, alkaloids, and anthocyanins (Song et al. 2009). Flavonoids in particular have been shown to have strong ARI activities (Grewal et al. 2016). Kim and Oh (1999) reported that extracts from the bark, wood, and leaves of *P. strobilacea* moderately inhibit AR activity (Kim and Oh 1999). Here, we showed that flower extracts from *P. strobilacea* have potent ARI activity. These results suggest that the bioactive compounds responsible for ARI activity in *P. strobilacea* extracts may be distributed in higher concentrations

in the flowers. These results demonstrate the potential use of MeOH extracts from the flowers of *A. japonica*, *M. bombycis*, and *P. strobilacea* as sources of ARIs. Further research characterizing the bioactive components of these plants will provide insights into their inhibitory activity against AR.

Quercetin (Fig. 1) is a flavonoid found ubiquitously in nature and is known to exhibit strong antioxidant properties and a wide range of biological activities, including anti-inflammatory, anti-diabetic, and anti-cancer effects (Deschner et al. 1991; Vessal et al. 2003; Boots et al. 2008; Yang et al. 2017; Ryu et al. 2018). The anti-diabetic properties of quercetin have been widely reported in literature in which several studies have reported quercetin as an AR inhibitor (Varma et al. 1975; Yawadio et al. 2007). The use of natural

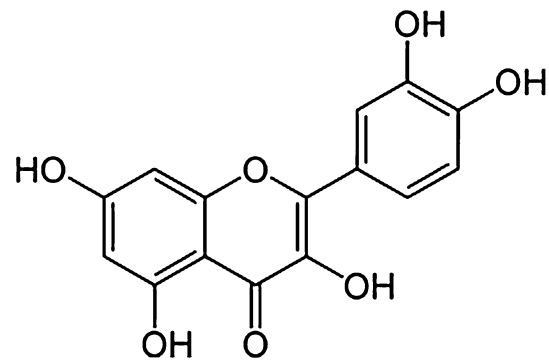


Fig. 1 Structure of quercetin

products such as quercetin not only alleviates the many disabling complications associated with diabetes but also provides protection against various diseases (e.g., cancer, osteoporosis, cardiovascular diseases) and promotes general well-being (Boots et al. 2008). Flavonoids are abundant

Table 6 IC₅₀ of purple flower extracts on rat lens AR

Sample	Concentration (μg mL ⁻¹)	Inhibition ^z (%)	IC ₅₀ ^v (μg mL ⁻¹)
<i>Agastache rugosa</i> ^w	10	66.03	2.36
	1	37.80	
	0.1	21.05	
<i>Aster koraiensis</i> ^w	10	83.73	4.60
	1	27.75	
	0.1	21.53	
<i>A. spathulifolius</i> ^w	10	70.33	1.21
	1	47.85	
	0.1	26.32	
<i>A. yomena</i> ^w	10	77.03	3.37
	1	44.50	
	0.1	32.54	
<i>Caryopteris incana</i> ^w	10	66.03	6.23
	1	32.06	
	0.1	18.66	
<i>Dicentra spectabilis</i> ^v	10	46.94	–
<i>Magnolia kobus</i> ^v	10	8.38	–
<i>Paulownia coreana</i> ^w	10	31.58	–
<i>Pseudosasa japonica</i> ^w	10	36.84	–
<i>Pueraria thunbergiana</i> ^w	10	46.41	–
<i>Syringa vulgaris</i> ^v	10	68.37	5.32
	1	35.71	
	0.1	26.53	
<i>Tulipa gesneriana</i> ^v	10	13.42	–
<i>Viola papilionacea</i> ^v	10	65.77	1.46
	1	44.97	
	0.1	30.87	
TMG ^x	10	99.62	0.17
	1	67.31	
	0.1	45.38	

Same as in Table 1

Table 7 Quercetin content of different flower extracts

Sample	Content (mg g ⁻¹ extract)
<i>Alnus japonica</i>	ND
<i>Aster spathulifolius</i>	ND
<i>Crysanthemum boreale</i>	1.56 ± 0.03
<i>Chaenomeles lagenaria</i>	ND
<i>Carpinus laxiflora</i>	ND
<i>Chionanthus retusus</i>	1.33 ± 0.01
<i>Morus bombycis</i>	ND
<i>Persicaria tinctoria</i>	0.82 ± 0.02
<i>Platycarya strobilacea</i>	ND
<i>Serratula coronata</i> var. <i>insularis</i>	3.37 ± 0.05
<i>Tulipa gesneriana</i> (red)	ND
<i>Viola papilionacea</i>	ND

ND not detected

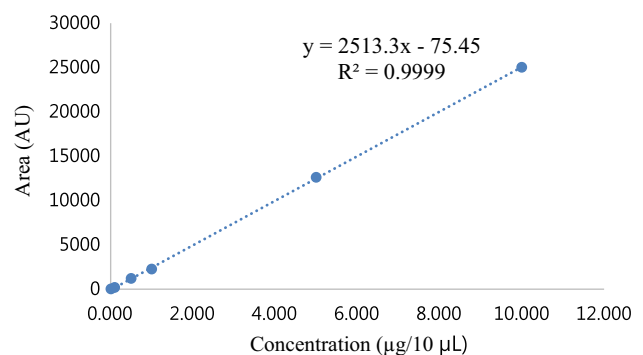


Fig. 2 Calibration curve for quercetin

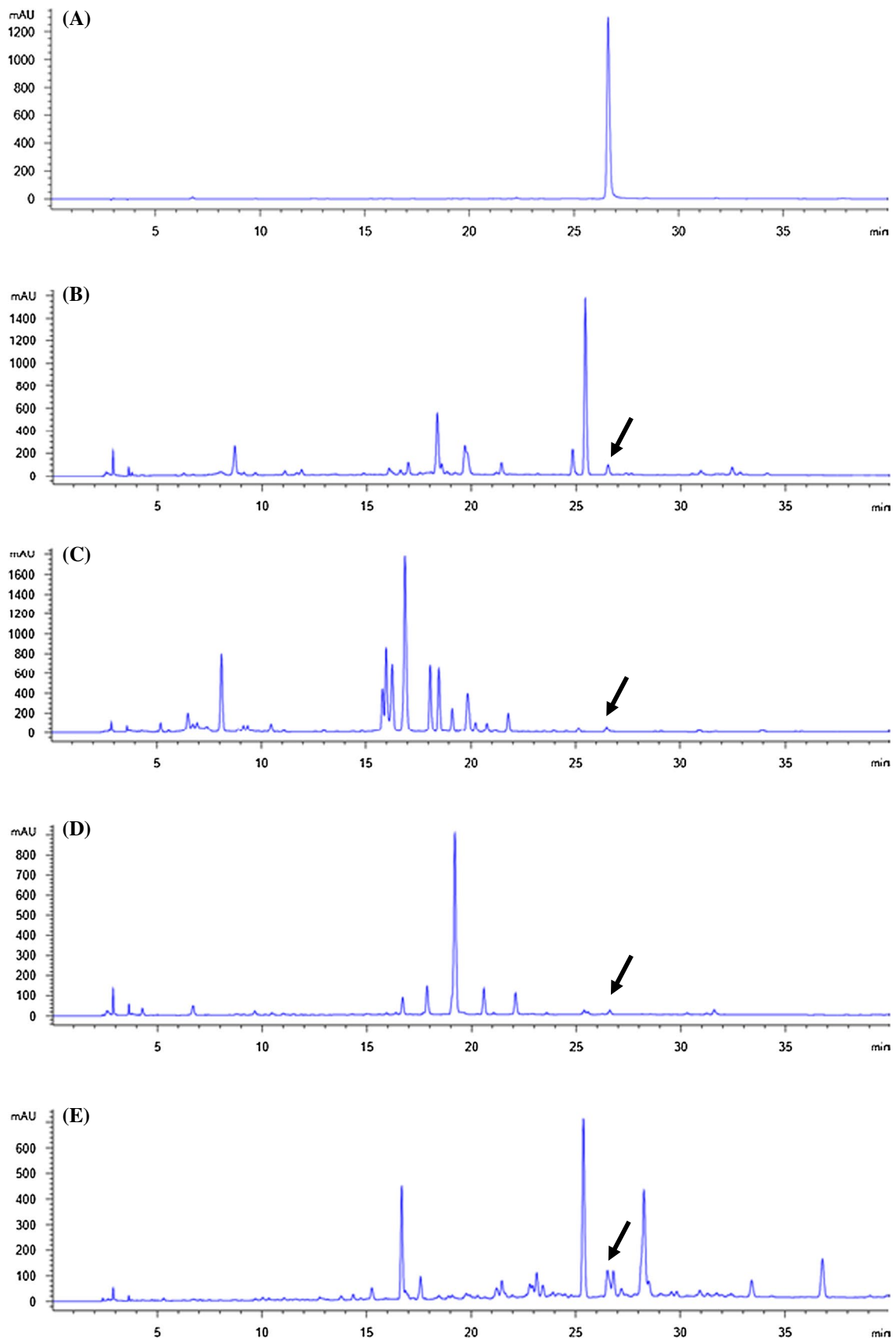


Fig. 3 HPLC chromatograms of quercetin (a), *C. boreale* (b), *C. retusus* (c), *P. tinctoria* (d), and *S. coronata* (e) (arrow means the peak of quercetin)

in flowers, and quercetin has been found in many flower extracts (Fossen et al. 1999; Swaroop et al. 2005). Hence, samples showing high ARI activities were further analyzed for quercetin content. A list of the samples analyzed with their respective quercetin content is shown in Table 7. The analytical method used for the chromatographic separation showed good linearity (Fig. 2, $r^2 = 0.9999$). Results show that quercetin was only detected in *C. retusus*, *C. boreale*, *P. tinctoria*, and *S. coronata* with concentrations of 1.33, 1.56, 0.82, and 3.37 mg g⁻¹ extract, respectively. In the remaining plant samples, the chromatograms show that other, possibly novel compounds are present, which may be responsible for their ARI activities (Fig. 3). For example, flowers of *Aster* and *Viola* spp. are rich in terpenoids and flavonoids that have been shown to exhibit high ARI activities in several studies (Lee et al. 2005; Morikawa 2007; Lee et al. 2017a, b). Similarly, *Chaenomeles*, *Tulipa* and *Carpinus* spp. are abundant in polyphenolic compounds, which may explain their high AR inhibition (Huang et al. 2013; Hofmann et al. 2016). Further studies regarding the bioactive components of these plants may elucidate the mechanism of their bioactive properties.

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