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ARTICLE

Pinoresinol Diglucoside is Screened as a Putative α-Glucosidase Inhibiting Compound in *Actinidia arguta* leaves

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Abstract *Actinidia arguta* leaves are consumed as a popular food material in Korea and have been reported to exert beneficial effects on humans due to its constituent polyphenolic compounds. In this study, the α-glucosidase inhibitory compounds in *A. arguta* were screened and identified through α-glucosidase-guided fractionation and metabolomic analysis. The 50% ethanol extracts of *A. arguta* showed strong inhibitory effect (32.6%), which was comparable to acarbose as a positive control (30.0%). Through multiple steps of fractionation, pinoresinol diglucoside and fertaric acid were identified as the major potent compounds in *A. arguta* inhibiting α-glucosidase activity by liquid chromatography mass spectrometry analysis and metabolomic comparison. Particularly, because pinoresinol and its glycosides have been demonstrated as α-glucosidase inhibitory agents, pinoresinol diglucoside was proposed to be a putative key compound for α-glucosidase inhibition in *A. arguta*. This is the first study demonstrating the anti-diabetic effect of a pinoresinol-containing fraction of *A. arguta* and would be useful for its application as a natural α-glucosidase inhibitor.

Keywords *Actinidia arguta* · α-glucosidase · liquid chromatography mass spectrometry · pinoresinol diglucoside

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Introduction

Diabetes mellitus (DM) is one of the most common chronic diseases that lead to death and disability worldwide (Beaglehole et al., 2007). In 2011, it has been estimated that approximately 366 million people live with diabetes and the incidence is expected to rise to 552 million by 2030 (Whiting et al., 2011). DM is a metabolic disease that has been associated with insufficient insulin secretion as well as when cells do not properly respond to the insulin or both (Shobana et al., 2009). Therefore, the management of blood glucose level is critical (Nathan et al., 2009) and the demand for therapeutic approaches to treat diabetes is continually increasing. One of the effective treatment approaches is to decrease the postprandial hyperglycemia that appears as high blood glucose levels after food intake by the inhibition of carbohydrate-hydrolyzing enzymes. α-Glucosidase is an essential enzyme responsible for converting carbohydrates to glucose in the small intestine and it can hydrolyze terminal non-reducing 1, 4-α-glucosidic linkages to release a single alpha-glucose molecule (Heo et al., 2009). Accordingly, α-glucosidase inhibitors play a critical role in delaying the digestion and absorption of carbohydrates for treatment of postprandial hyperglycemia and thus have a hypoglycemic effect (van de Laar et al., 2005). Although synthetic antidiabetic agents such as acarbose and voglibose have been proven as powerful α-glucosidase inhibitors for clinical application, some side effects such as diarrhea, flatulence, and abdominal discomfort have been reported (Chaisson et al., 2002). Hence, studies have focused on the purification and identification of α-glucosidase inhibitors from natural resources, and more than 800 plant species have now been identified to possess potent inhibitory compounds against α-glucosidase (Perez et al., 1998; Liu et al., 2011).

Edible wild herbs have been traditionally used as food ingredients in Korea. These are high in fiber, minerals, and phytochemicals such as carotenoids, flavonoids, phenolic acids, terpenoids, and lignans (Webby et al., 1990; Craig et al., 1999; Apati et al., 2004;

Jang et al., 2009), and various pharmacological efficacies had been reported, i.e., antioxidant, anti-inflammatory, anti-aging, and antibacterial activities (Lee et al., 2007; Starks et al., 2010). *Actinidia arguta*, which belongs to the family Actinidiaceae, mostly grows in China, Korea, Siberia, and Japan. *A. arguta* extracts have been reported to impart antiallergenic and anti-inflammatory effects (Park et al., 2005; Kim et al., 2009), and the proliferation-promoting effects of (+)-catechin and (−)-epicatechin from the stems of *A. arguta* have also been described (Takano et al., 2003). Recently, components of *A. arguta* (hardykiwi and leaf) were found to be useful in DM; however, the systemic analysis of its key compounds has not been conducted (Shirosaki et al., 2008; Kurakane et al., 2011; Kim et al., 2013).

Metabolomics is a new emerging tool for non-targeted profiling and identification of all metabolites in samples under a given set of conditions and thus is being applied to various studies involving the comprehensive analysis of plants (Bino et al., 2004). The collected data are subjected to multivariate statistical analysis by principal component analysis (PCA), partial least-squares discriminatory analysis (PLS-DA), or orthogonal PLS-DA (OPLS-DA) to classify the data set to different groups and effective discriminants could be easily screened.

In this study, we evaluated the anti-diabetic effect of *A. arguta in vitro* based on α-glucosidase inhibition and screened active compounds by partial purification through preparative reverse phase liquid chromatography. Key compounds were tentatively identified by High-performance liquid chromatography (HPLC)-ion trap-ESI-MS/MS using multivariate statistical analysis.

Materials and Methods

Preparation of *A. arguta* extract. The dried leaves of *A. arguta* (1 g) were extracted with 200 mL of solvent (water, 50% ethanol, and 100% ethanol) at room temperature for 12 h. The supernatant was collected after centrifugation at 7,000×*g* for 5 min (Hanil® combi-514R, Korea) and filtered (Whatman No. 1 paper, GE Healthcare, UK). The filtrate was concentrated by a rotary evaporator (Eyela, Japan) and then lyophilized, and the dried extracts were kept at −80°C until further experiments.

Determination of α-glucosidase inhibitory activity *in vitro*. The dried extracts were dissolved in distilled water at concentrations of 0.045 and 0.09 mg/mL, and the *in vitro* α-glucosidase inhibitory activity was assessed according to the method of Watanabe et al. (1997), with modifications. Yeast α-glucosidase (0.7 unit/mL) and 5 mM of *p*-nitrophenyl-α-D-glucopyranoside (Sigma Co., USA) dissolved in potassium phosphate buffer (50 mM, pH 6.8) were used as an enzyme solution and a substrate solution, respectively. The enzyme solution (50 μL) and 10 μL of the samples were mixed, and then incubated at 25°C for 5 min. After a 5-min pre-incubation, 50 μL of the substrate solution was added and reacted for 5 min, and the absorbance at 405 nm was measured with a microplate reader (SpectraMax 190, Molecular Devices, USA). The inhibitory activity was calculated as a percentage of the blank control.

Partial purification of *A. arguta* extracts using preparative liquid chromatography. The 50% ethanol extracts of *A. arguta* were fractionated using preparative LC (LC-Forte/R, YMC, Japan) equipped with double plunger pump and UV detector (200–400 nm). Stepwise procedures for the fractionation were carried out using different gradients of acetonitrile with reverse phase liquid chromatography (YMC-DispoPack AT C18, 50 μm; C18 column, 20 μm, 15×250 mm, YMC) and is summarized in Fig. 1. The 50% ethanol extracts suspended in water were separated into 1–4 fractions by reverse phase liquid chromatography (YMC DispoPack AT, YMC), and fraction 2, as an active fraction, was further purified. Fraction 2 was separated into fractions 1–4 again, and the active fractions (2–2 and 2–3) were combined and purified into 1–5 subfractions. Finally, subfraction 3–1 was prepared as a partially purified fraction of *A. arguta* extract and analysed.

Liquid chromatography mass spectrometry (LC-MS/MS) analysis. Samples were analyzed using an Accela HPLC system with a PDA Detector (Accela 80 Hz PDA detector) and a LTQ-Velos ion trap mass spectrometer fitted with a heat electrospray ionization interface (Thermo Fisher Scientific, USA) equipped with a C18 column (1.9 μm, 2.0×100 mm, Triart, YMC). The elution gradient was established by using a binary solvent system consisting of 0.1% formic acid in water (solvent A) and 0.1% formic acid in acetonitrile (solvent B) at a constant flow rate of 0.3 mL/min. The linear gradient profile was as follows: 5–50% of solvent B over 10 min, 50–90% of solvent B over 20 min, held at a 90% solvent B for another 10 min, then returned to the initial conditions (5% of solvent B) in 10 min, and finished at 50 min. The column temperature was 36°C, and the UV spectra were measured between 180 and 800 nm. Acquisition was performed in the negative and positive modes by electrospray ionization (ESI) source, and the scanned range of m/z was 100–1,000 Da. The source voltage was 5 kV for both negative and positive ionizations, capillary temperature was 275°C with sheath gas at 35 units and auxiliary gas at 5 units.

Data processing and analysis for metabolite identification. Peak detection, alignment, and identification were performed using the SIEVE software (Thermo Fisher Scientific) with frame parameters as follows: a m/z width of 2, a retention time width of 2.5 min, a noise threshold of 10,000, and a correlation bin width of 2. The acquired results were subjected to multivariate statistical analysis using SIMCA (Umetrics, Sweden). PCA was used to visualize the similarities and differences between samples, and the orthogonal partial least squared discriminant analysis (OPLS-DA) was applied to detect maximal separation of distinctive metabolites in each partially purified fractions. The MS/MS fragmentation patterns were used for informative non-targeted metabolic profiling of LC-MS data and the acquired LC-MS/MS spectrum was identified after the comparison with those proposed by the Massbank database (www.massbank.jp), KEGG database (www.kegg.co.jp), Metlin (http://masspec.scripps.edu) and related reports.

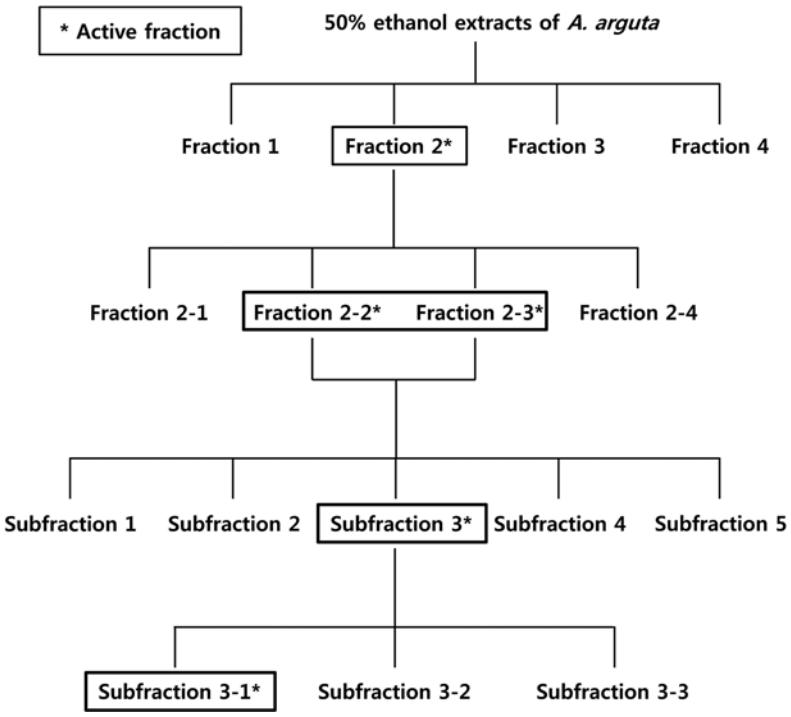

Fig. 1 Experimental procedures for partial purification α-glucosidase inhibitory compounds in 50% ethanol extracts from *Actinidia arguta* using preparative liquid chromatography.

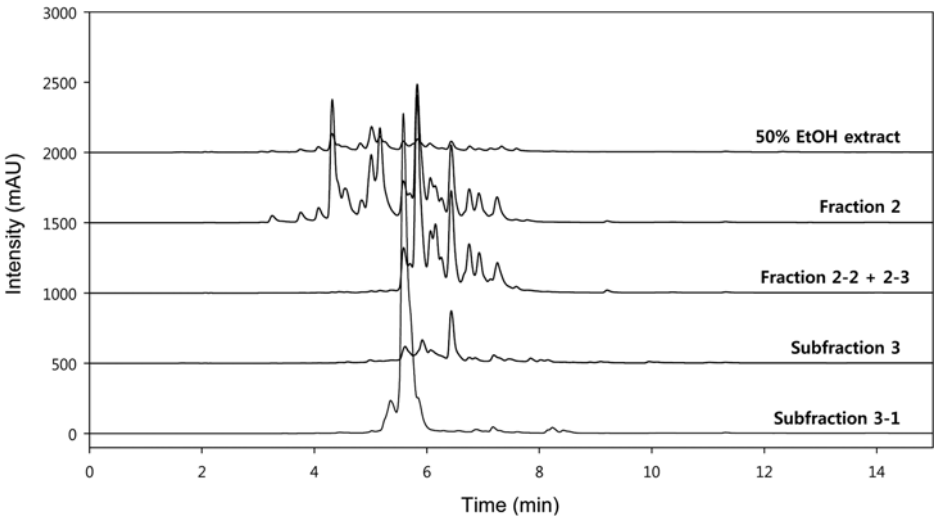

Fig. 2 HPLC chromatograms for the active fractions from *Actinidia arguta* extracts. Samples were analyzed using a reverse phase column with UV detector (320 nm) under the conditions described in Methods.

Results

α-Glucosidase inhibitory activity of *A. arguta* extract. The α-glucosidase inhibitory activities of *A. arguta* extracts were compared at a concentration of 0.9 mg/mL. Among the three different solvent extracts (water, 50% ethanol, and 100% ethanol), the 50% ethanol extract exhibited the highest inhibitory activity on α-glucosidase as 61.6±5.51%, whereas 9.5±1.90% and 17.97 ±3.16% were indicated in water and 100% ethanol extracts, respectively. Thus, 50% ethanol was selected as the most effective solvent for the extraction of α-glucosidase inhibitory compounds from *A. arguta*. Inhibitory activity of the 50% ethanol extract at a concentration of 0.23 mg/mL (32.6±5.77%) was comparable to the same level of the positive control, acarbose (30.0±1.10%), which indicated that *A. arguta* is a natural resource with anti-diabetic activity.

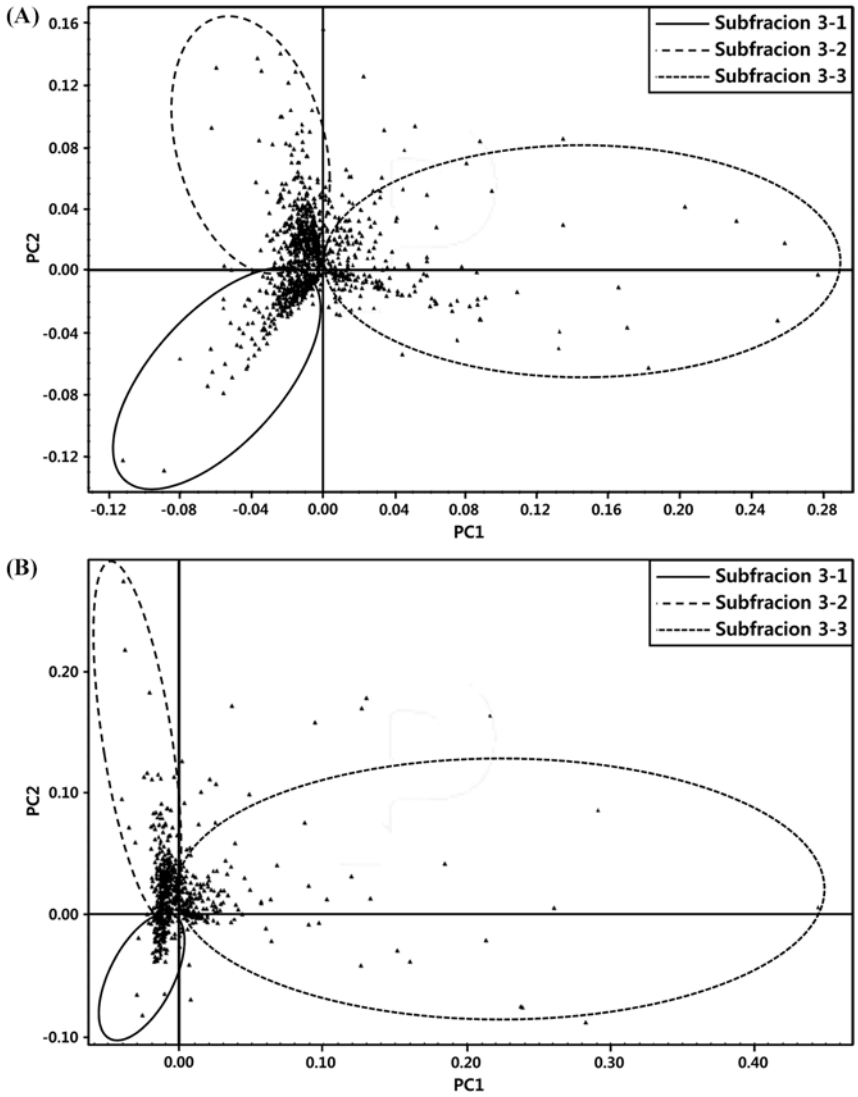

Fig. 3 Loading scatter plot of the metabolites in sub-fractions (3-1, 3-2, and 3-3) analyzed by LC-ESI-ion trap-MS/MS. A, negative ion mode; B, positive ion mode.

Partial purification of *A. arguta* extracts using preparative liquid chromatography. The 50% ethanol extracts of *A. arguta* indicated a potent inhibitory activity on α-glucosidase, thus we partially purified the extracts of *A. arguta* using *in vitro* enzyme assay-guided fractionation (Fig. 1). First, 50% ethanol extracts were subjected to DispoPack AT (50 μm, YMC) eluted with a solvent gradient system to yield four fractions (F1–4). The α-glucosidase inhibitory activities of each fractions (F1–4) were 10.6±4.1, 80.8±3.4, 29.7±2, and 16.6±0.7%, respectively, and F2 eluted with acetonitrile gradient between 32–50% was subjected to the next step separation. F2 was subjected to C18 column (20 μm, 15×250 mm, YMC) to generate four fractions (F2-1–4) and the α-glucosidase inhibitory activity of each fractions were 4.4±2.1, 59.1±3.9, 63.2±1.0, and 26.5±4.1%, respectively. F2-2 (eluted with 23–8% acetonitrile) and F2-3 (eluted with 28–37% acetonitrile) exhibited strong α-glucosidase inhibitory activity, and these were combined and further fractionated into five subfractions (sub1–5). Sub3 showed the highest α-glucosidase inhibition at 58.0±3.1%, and this active fraction was applied on a C18 column eluted with a solvent gradient of acetonitrile (1,525%) to yield four sub-fractions (sub3-1–4). Each sub-fraction showed an inhibition of α-glucosidase at 82.5±4.6, 73.9±5.9, 34.3±9.0, and 0.1±7.7%, respectively. Through the partial purification of the 50% ethanol extract, sub-fraction 3-1 was collected as a fraction containing potent inhibitory compounds against α-glucosidase.

Identification of the active compounds responsible for α-glucosidase inhibitory activity of *A. arguta*. All samples fractionated from *A. arguta* extract were analyzed by HPLC (Fig. 2). According to the purification steps, the number of peaks decreased and the intensity increased. The major peaks of final

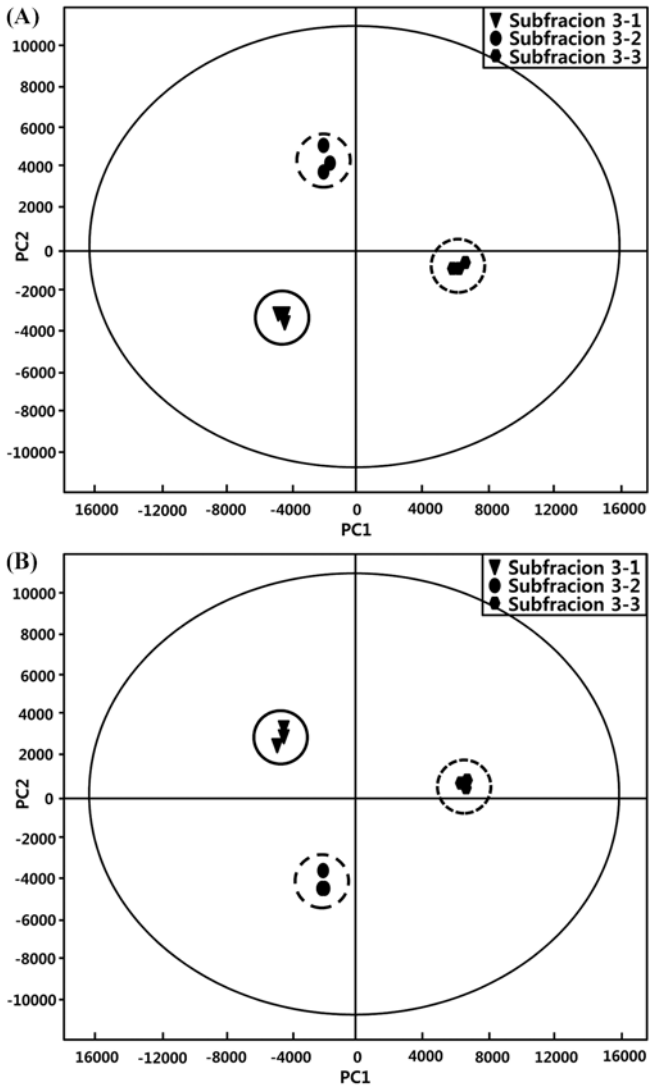

Fig. 4 Principal component analysis (PCA) of the metabolites in sub-fractions (3-1, 3-2, and 3-3) analyzed by LC-ESI-ion trap-MS/MS. A, negative ion mode; B, positive ion mode.

fractions (sub3-1) exhibited relatively higher intensity at 5–6 min and consequently sub3-1 was supposed to contain the active compounds responsible for the observed anti-diabetic effect. Purified fractions (sub3-1, 3-2, and 3-3) were analyzed by LC-ESI-ion trap-MS/MS and the metabolites in each fraction were processed through multivariate statistical analysis to discriminate the different metabolites in each fraction. The loading scatter plot is indicated in Fig. 3, which shows the correlation between the variables. It was clearly observed that the active fraction, sub3-1, was on the left side of the lower part and separated from sub3-2 and sub3-3. PCA is the most commonly used unsupervised multivariate analysis in metabolomic studies, and the similarities and differences among sub-fractions were visually assessed (Fig. 4). The replicates of each sample clustered closely together, and sub3-1 was found as the active fraction that was clearly separated from the other sub-fractions (sub3-2, sub3-3). In negative ion mode, the metabolites in sub3-1 were discriminated from sub3-2 by component 2 (31.7%), sub3-1 by component 1 (66.6%), and similar results were obtained in positive ion mode. From the total ion chromatogram (TIC) of the sub-fractions, the major peaks of sub3-1 were detected at 5 min (Fig. 5), whereas the major peaks of sub3-2 and sub3-3 were detected at 5.5–7 min. The OPLS-DA screened highly significant metabolites contained in the fraction sub3-1 and the compounds with α-glucosidase inhibitory activity was further identified. As a result, pinoresinol-diglucoside and fertaric acid were successfully screened as the highly significant key compounds in sub 3-1. These compounds are presented in Table 1. The structure and proposed fragmentation pathway of identified compounds are shown in Fig. 6. Pinoresinol-diglucoside had a $[M-H]^-$ ion at m/z 681.21, which fragmented into daughter ions at m/z 519.04 (-glucoside) and 357.04 (-glucoside), indicated as pinoresinol fragment. Pinoresinol is a lignan widely distributed in plant-derived foods including fruit, vegetables, and cereals. Plant lignans have been known to be beneficial to human health, and pinoresinol imparts antioxidant activity, as well as hepato-protective and hypoglycemic effects (Gulcin et al., 2006; Kim et al., 2010; Wikul et al. 2012). Fertaric acid had a $[M-H]^-$ ion at m/z 325.11 that is fragmented into daughter ions at m/z 192.95 (-tartaric acid), 177.94, 148.99, and 133.93. Fertaric acid is an ester formed from ferulic acid that is bound to tartaric acid and is one of the hydroxycinnamic acids and ferulic acids that have reported as precursors of pinoresinol (Wikul et al., 2006; Adisakwattana et al., 2009).

Discussion

The incidence of type-2 diabetes, which is characterized by the relative insulin deficiency, fasting, and postprandial hyperglycemia, is rapidly increasing worldwide (Chakrabarti et al., 2002). One of the treatments for type-2 diabetes is inhibiting carbohydrate-hydrolyzing enzymes that break carbohydrates into absorbable monosaccharides. Acarbose, for instance, is an effective α-glucosidase inhibitor for the management of hyperglycemia (Hanafeld et al., 1998). However, many studies have focused on the identification of safe alternative agents from foods such as fruits and medicinal plants due to their low risk for side effects (Toeller et al., 1994; Bhandari et al., 2008; Choi et al., 2010; Kurakane et al., 2011).

In the present study, the α-glucosidase inhibitory compounds in *A. arguta* were screened and identified through metabolomics analysis of partially purified fractions. Pinoresinol diglucoside and fertaric acid were identified as the major potent compounds of *A. arguta* that inhibit α-glucosidase activity. Shirosaki et al. (2008) described the anti-hyperglycemic activity of *A. deliciosa* in mice and proposed possible contributions of polyphenols as active compounds. Recently, Kurakane et al. (2011) also confirmed the

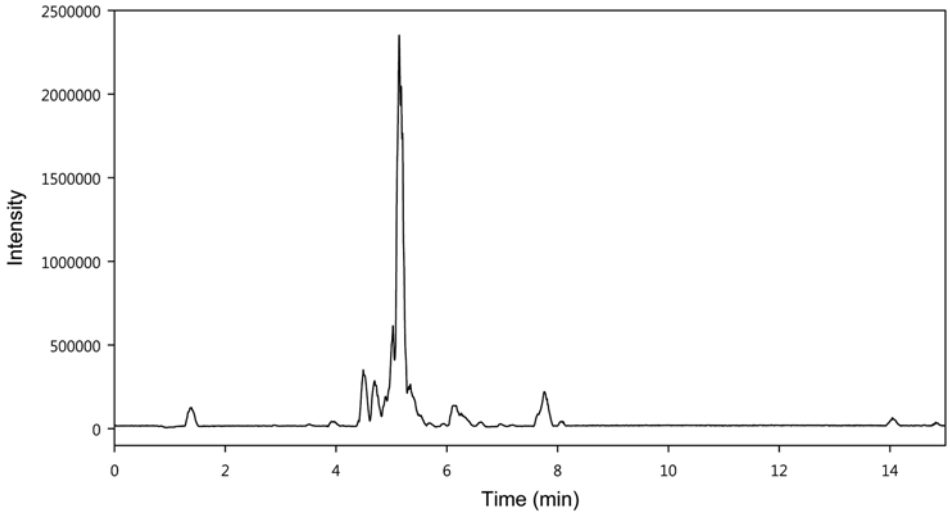

Fig. 5 Total ion chromatogram (TIC) of the active fraction, sub-fraction 3-1, in negative mode ion mode analyzed by LC-ESI-ion trap-MS/MS.

Table 1 Tentative identification of the key metabolites in sub-fraction 3-1 by LC-ESI-ion trap-MS/MS

m/z	Retention time (min)	ms/ms	Tentative identification	Formula
325.11	5.1	192.95, 177.94, 148.99	Fertaric acid	$C_{14}H_{14}O_9$
681.21	5.2	519.04, 357.04	Pinoresinol diglucoside	$C_{32}H_{42}O_{16}$

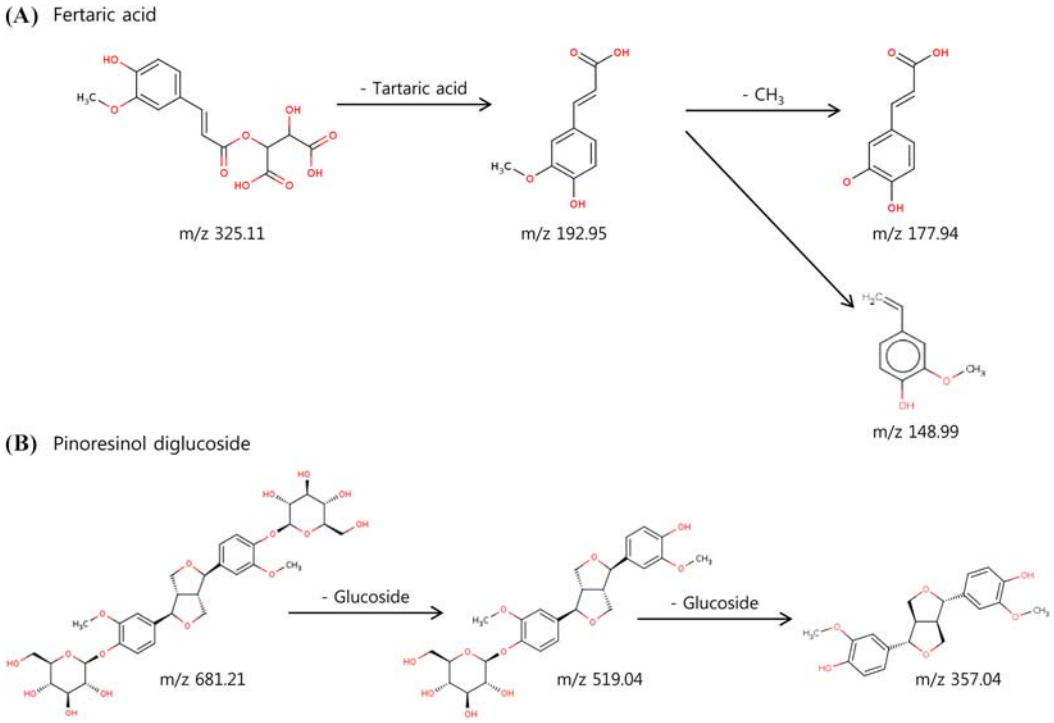

Fig. 6 Proposed fragmentation pathways for fertaric acid (A) and pinoresinol-diglucoside (B) by LC-ESI-ion trap-MS/MS.

anti-diabetic effects of *A. arguta* and revealed that the polyphenol fraction containing isoquercetin and hyperoside would be active contributors to their anti-diabetic effect. Pinoresinol and its glycosides were not reported as functional compounds in *A. arguta*. Although it was detected in the root extract of *A. arguta*, pinoresinol was not indicated as a main contributor for anti-glycation activity that is one of the diabetic complications (Jang et al., 2009). However, Wikul et al. (2012) proposed pinoresinol as

a potent hypoglycemic agent in defatted sesame by α-glucosidase inhibition, and the inhibition mechanism was clearly elucidated. Pinoresinol demonstrated inhibitory effect against α-glucosidase with mixed-type inhibition identical to ferulic acid, a proposed precursor of pinoresinol, which occurs as fertaric acid, an ester form with tartaric acid in the present study. Therefore, we successfully concluded that pinoresinol is a potent hypoglycemic compound in *A. arguta* that would impart a synergistic effect with fertaric acid; thus further investigations on its characterization are warranted. This is the first study to demonstrate the anti-diabetic effect of a pinoresinol-containing fraction of *A. arguta*, which would be useful for the possible application of *A. arguta* as a natural α-glucosidase inhibitor.

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