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Short Communication

Inhibitory Effects of Dicaffeoylquinic Acids from *Artemisia dubia* on Aldo-keto Reductase Family 1B10

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The ethyl acetate fraction of *Artemisia dubia* showed a potent inhibitory activity on recombinant human AKR1B10 (rh AKR1B10). Due to its potency, subsequent purification of ethyl acetate fraction led to seven compounds including five dicaffeoylquinic acid (DCQA) derivatives. Compounds were identified as 3,4-dihydroxybenzoic acid (1), quercetin 3-*O*-β-glucose (2), 3,4-DCQA (3), 3,5-DCQA (4), 4,5-DCQA (5), 3,5-DCQA methyl ester (6), and 4,5-DCQA methyl ester (7). A series of DCQA derivatives (3-7) showed inhibitory activity on rhAKR1B10 in the range of IC_{50} 1.24-2.29 μM, whereas 3,4-dihydroxybenzoic acid and quercetin 3-*O*-β-glucose showed no inhibitory activity on rhAKR1B10.

Key words: AKR1B10, aldose reductase-like, anticancer, DCQA, dicaffeoylquinic acid, *Artemisia dubia*

AKR1B10, a member of the aldo-keto reductase (AKR) family, participates in the reduction of various aldehydes and ketones including retinals, farnesal, and geranylgeranial [Cao *et al.*, 1998; Crosas *et al.*, 2003]. Numerous reports showed that AKR1B10 is highly expressed in various types of cancer cells including hepatocellular carcinoma, lung squamous cell carcinoma, lung adnocarcinoma in smokers, and cervical cancer [Fukumoto *et al.*, 2005; Yoshitake *et al.*, 2007; Heringlake *et al.*, 2010]. Furthermore, current studies have shown that knock-down of AKR1B10 gene results in antiproliferation of certain types of cancer cells. The down-regulation of AKR1B10 mRNA inhibited colorectal cancer cell growth by enhancing susceptibility to reactive carbonyls such as acrolein and crotonaldehyde [Yan *et al.*, 2007]. Another study reported that inhibition of AKR1B10 promoted cell death by disrupting lipid biosynthesis and mitochondrial functions, which are essential for cell survival [Ma *et al.*, 2008; Wang *et al.*, 2009]. Thus, AKR1B10 is thought to be a potential cancer therapeutic target. However, specific AKR1B10 inhibitors have not been used clinically to date.

In the present study, seven major compounds of the ethyl acetate fraction of *Artemisia dubia* were isolated and tested for inhibitory activity on AKR1B10 using rhAKR1B10. *A. dubia* is one of the Korean wild vegetables consumed as young leaves since ancient times. Many *Artemisia* species are known to be very effective for treatment of various diseases including cancer [Kim *et al.*, 2006; Lai and Singh, 2006; Ntutela *et al.*, 2009]. The most popular example is *A. annua*, in which terpenoids and their derivatives have been developed as potent antimalaria drugs and are currently used in clinics [Dhingra *et al.*, 2000]. Although *A. dubia* is an endemic plant in Korea, its biological effects have not yet been examined. In the present study, a series of DCQA compounds isolated from *A. dubia* were found to have inhibitory activity on AKR1B10, which could be considered as a potential cancer chemotherapeutic target.

Aerial parts of *A. dubia* WALL. were collected at the Wild Vegetable Experiment Station, Gangwon ARES, Korea. The voucher specimen (D-050) was stored at the Natural Products Research Center, KIST Gangneung Institute, Gangneung, Korea. Dried *A. dubia* (1.7 kg) was extracted three times by refluxing with 94% ethanol for 3 h. The residue was evaporated under reduced pressure to yield the ethanol extract (70 g). The extract was suspended in distilled water and sequentially partitioned with *n*-hexane, ethyl acetate, and *n*-butanol. Seven compounds

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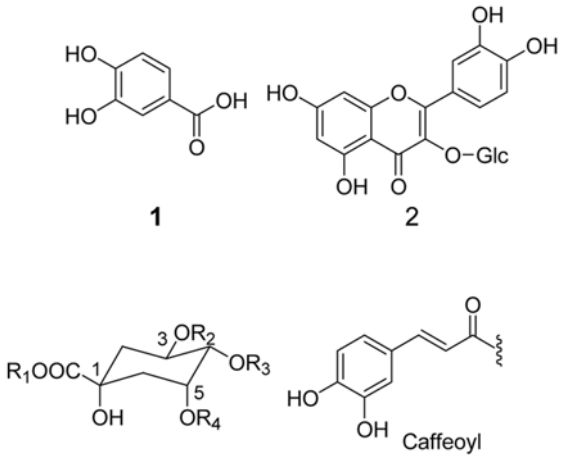

Compound	R_1	R_2	R_3	R_4
3	H	Caffeoyl	Caffeoyl	H
4	H	Caffeoyl	H	Caffeoyl
5	H	H	Caffeoyl	Caffeoyl
6	Me	Caffeoyl	H	Caffeoyl
7	Me	H	Caffeoyl	Caffeoyl

Fig. 1. The structures of major compounds isolated from *A. dubia*.

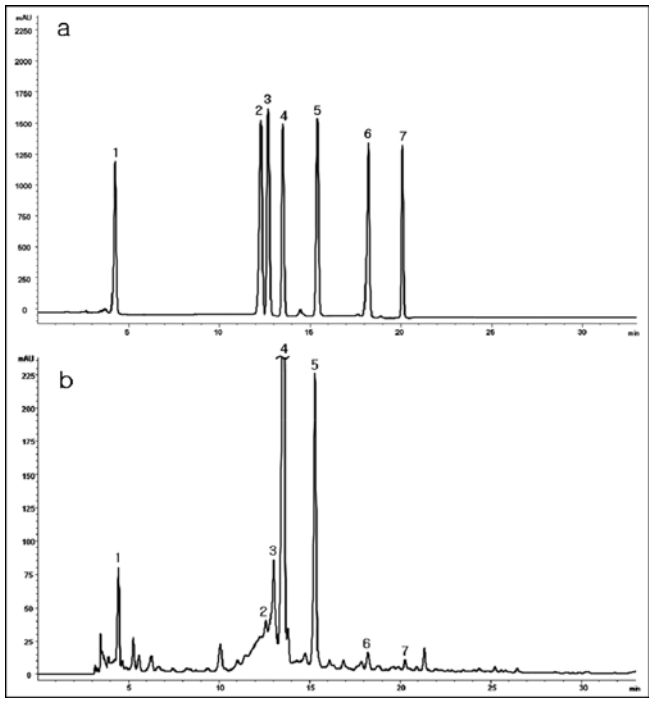

Fig. 2. HPLC chromatograms of the isolated compounds (a) and ethyl acetate fraction (b) recorded at 254 nm. Each peak number corresponds to the compound having the same number in Fig. 1.

were isolated from ethyl acetate fraction of *A. dubia* (Fig. 1), and their contents in the ethanol extract and ethyl acetate fraction were examined (Table 1) by HPLC (Fig. 2). The chemical structures of seven compounds were identified by ^{1}H- and ^{13}C-NMR spectroscopies and confirmed by comparison of NMR data with the literatures values [Basnet *et al.*, 1996; Teng *et al.*, 2005].

3,4-Dihydroxybenzoic acid (1). ^{1}H-NMR (500 MHz, MeOH-d_4) δ: 7.43 (1H, d, *J*=2.2 Hz, H-2), 7.41 (1H, dd, *J*=2.2, 8 Hz, H-6), 6.80 (1H, d, *J*=8 Hz, H-5). ^{13}C-NMR (125 MHz, MeOH-d_4) δ: 168.82 (COOH), 150.12 (C-4), 144.65 (C-3), 122.45 (C-6), 121.70 (C-1), 116.28 (C-2), 114.32 (C-5).

Quercetin-3-*O*-β-glucoside (2). ^{1}H-NMR (500 MHz, DMSO-d_6) δ: 7.58 (2H, s, H-2', 6'), 6.84 (1H, d, *J*=9.3 Hz, H-5'), 6.39 (1H, s, H-8), 6.19 (1H, s. H-6), 5.46 (1H, d, *J*=7.7 Hz, H-1"). ^{13}C-NMR (125 MHz, DMSO-$d6_4$) δ: 177.88 (C-4), 164.64 (C-7), 161.68 (C-5), 156.76 (C-9), 156.59 (C-2), 148.93 (C-4'), 145.27 (C-3'), 133.74 (C-3), 122.05 (C-6'), 121.59 (C-1'), 116.62 (C-2'), 115.65 (C-5'), 104.39 (C-10), 101.27 (C-1"), 99.11 (C-6), 93.95 (C-8), 78.04 (C-5"), 76.93 (C-3"), 74.53 (C-2"), 70.36 (C-4"), 61.41 (C-6").

3,4-Dicaffeoylquinic acid (3). ^{1}H-NMR (500 MHz, MeOH-d_4) δ: 7.58 (2H, t, *J*=15.4 Hz, H-7', 7"), 7.03 (2H, d, *J*=1.9 Hz, H-2', 2"), 6.93 (2H, dd, *J*=1.9, 8.2 Hz, H-6', 6"), 6.77 (2H, d, *J*=8.2 Hz, H-5', 5"), 6.29 (2H, t, *J*=16.3 Hz, H-8', 8"), 5.63 (1H, m, H-3), 4.99 (1H, m, H-4), 4.37 (1H, m, H-5), 2.11-2.36 (4H, m, H-2, 6). ^{13}C-NMR (125 MHz, MeOH-d_4) δ: 176.62 (COOH), 167.20 (C-9', 9"),

Table 1. Composition of the compounds isolated from the ethanol extract and ethyl acetate fraction of *A. dubia*

Compounds	Ethanol extract (μg/mg)[a]	Ethyl acetate fraction (μg/mg)[a]
3,4-Dihydroxybenzoic acid (**1**)	1.75±0.02	15.15±0.15
Quercetin 3-*O*-β-Glc (**2**)	7.05±0.02	43.67±0.67
3,4-Dicaffeoylquinic acid (**3**)	19.90±0.92	94.17±2.27
3,5-Dicaffeoylquinic acid (**4**)	51.80±1.06	262.28±4.07
4,5-Dicaffeoylquinic acid (**5**)	17.04±0.31	93.97±1.32
3,5-DCQA methyl ester (**6**)	not detected	4.43±0.84
4,5-DCQA methyl ester (**7**)	not detected	2.01±0.55

[a)]Data are presented as means±SD, *n*=3.

148.22 (C-4', 4"), 145.97 (C-7', 7"), 145.41 (C-3', 3"), 126.36 (C-1', 1"), 121.82 (C-6', 6"), 115.06 (C-5', 5"), 113.82 (C-2', 2"), 113.49 (C-8', 8"), 75.29 (C-4), 73.79 (C-1), 68.72 (C-3), 64.37(C-5), 40.57 (C-2), 35.63 (C-6).

3,5-Dicaffeoylquinic acid (4). ^{1}H-NMR (500 MHz, MeOH-d_4) δ: 7.60 (1H, d, *J*=16 Hz, H-7'), 7.56 (1H, d, *J*=16 Hz, H-7"), 7.07 (2H, d, *J*=2.3 Hz, H-2', 2"), 6.99 (2H, dd, *J*=2.3, 8.3 Hz, H-6', 6"), 6.79 (2H, d, *J*=8.3 Hz, H-5', 5"), 6.37 (1H, d, *J*=16 Hz, H-8'), 6.29 (1H, d, *J*=16 Hz, H-8"), 5.45 (1H, m, H-5), 5.40 (1H, m, H-3), 3.99 (1H, m H-4), 2.23-2.34 (4H, m, H-2, 6). ^{13}C-NMR (125 MHz, MeOH-d_4) δ: 176.09 (COOH), 167.47 (C-9'), 166.95 (C-9"), 148.20 (C-4',4"), 145.86 (C-7'), 145.63 (C-7"), 145.38 (C-3',3"), 126.50 (C-1',1"), 121.66 (C-6',6"), 115.05 (C-5',5"), 114.17 (C-8'), 113.80 (C-2',2"), 113.68 (C-8"), 73.34 (C-1), 71.15 (C-5), 70.68 (C-3), 69.27 (C-4), 36.29 (C-2), 34.62 (C-6).

4,5-Dicaffeoylquinic acid (5). ^{1}H-NMR (500 MHz, MeOH-d_4) δ: 7.62 (1H, d, *J*=16 Hz, H-7'), 7.54 (1H, d, *J*=16 Hz, H-7"), 7.03 (2H, d, *J*=2.3 Hz, H-2', 2"), 6.93 (2H, dd, *J*=2.3, 8.3 Hz, H-6', 6"), 6.76 (2H, d, *J*=8.3 Hz, H-5', 5"), 6.31 (1H, d, *J*=15.9 Hz, H-8'), 6.21 (1H, d, *J*=15.9 Hz, H-8"), 5.63 (1H, m, H-5), 5.11 (1H, m, H-4), 4.37 (1H, m, H-3), 2.12-2.28 (4H, m, H-2, 6). ^{13}C-NMR (125 MHz, MeOH-d_4) δ: 175.45 (COOH), 167.13 (C-9'), 166.80 (C-9"), 148.27 (C-4', 4"), 146.92 (C-7'), 146.17 (C-7"), 145.36 (C-3', 3"), 126.28 (C-1', 1"), 121.74 (C-6', 6"), 115.05 (C-5', 5"), 113.74 (C-2', 2"), 113.32 (C-8'), 113.26 (C-8"), 74.36 (C-4), 74.31 (C-1), , 67.94 (C-3), 67.59 (C-5), 37.94 (C-6), 37.02 (C-2).

3,5-Dicaffeoylquinic acid methyl ester (6). ^{1}H-NMR (500 MHz, MeOH-d_4) δ: 7.64 (1H, d, *J*=16 Hz, H-7'), 7.57 (1H, d, *J*=16 Hz, H-7"), 7.07 (2H, d, *J*=2.3 Hz, H-2', 2"), 6.99 (2H, d, *J*=2.3, 8.3 Hz, H-6', 6"), 6.80 (2H, d, *J*=8.3 Hz, H-5', 5"), 6.36 (1H, d, *J*=16 Hz, H-8'), 6.24 (1H, d, *J*=16 Hz, H-8"), 5.40 (1H, m, H-5), 5.38 (1H, m, H-3), 3.99 (1H, m, H-4), 3.70 (3H, s, OMe), 2.21-2.36 (4H, m, H-2, 6). ^{13}C-NMR (125 MHz, MeOH-d_4) δ: 174.20 (COOMe), 167.32 (C-9'), 166.51 (C-9"), 148.37 (C-4', 4"), 146.06 (C-7'), 145.74 (C-7"), 145.48 (C-3', 3"), 126.44 (C-1', 1"), 121.67 (C-6', 6"), 115.13 (C-5', 5"), 114.00 (C-8'), 113.69 (C-2', 2"), 113.40 (C-8"), 73.20 (C-1), 70.79 (C-3), 70.53 (C-5), 68.35 (C-4), 51.61 (OMe), 35.35 (C-2), 34.22 (C-6).

4,5-Dicaffeoylquinic acid methyl ester (7). ^{1}H-NMR (500 MHz, MeOH-d_4) δ: 7.62 (1H, d, *J*=16 Hz, H-7'), 7.52 (1H, d, *J*=16 Hz, H-7"), 7.04 (2H, d, *J*=2.4 Hz, H-2', 2"), 6.95 (2H, d, *J*=2.3, 8.2 Hz, H-6', 6"), 6.77 (2H, d, *J*=8.3 Hz, H-5', 5"), 6.32 (1H, d, *J*=16 Hz, H-8'), 6.19 (1H, d, *J*=16 Hz, H-8"), 5.54 (1H, m, H-5), 5.13 (1H, m, H-4), 4.36 (1H, m, H-3), 3.72 (3H, s, OMe), 2.24-2.35 (4H, m, H-2, 6). ^{13}C-NMR (125 MHz, MeOH-d_4) δ: 173.76 (COOMe), 167.05 (C-9'), 166.46 (C-9"), 148.38 (C-4', 4"), 146.31 (C-7', 7"), 145.42 (C-3', 3"), 126.26 (C-1'), 126.10 (C-1"), 121.75 (C-6', 6"), 115.09 (C-5', 5"), 113.73 (C-2', 2"), 113.28 (C-8'), 113.10 (C-8"), 74.32 (C-4), 74.04 (C-1), 67.66 (C-5), 67.13 (C-3), 51.68 (OMe), 36.96 (C-2, 6).

The rhAKR1B10 was prepared as reported previously [Lee *et al.*, 2009]. Briefly, reaction mixtures consisted of 0.1 M potassium phosphate (pH 7.0), 0.16 mM NADPH, 2 μM of rhAKR1B10 with varied concentrations of substrate DL-glyceraldehyde, and test sample in a total volume of 200 μL. The rhAKR1B10 activity was assayed spectrophotometrically by measuring the decrease in absorption of NADPH at 340 nm after substrate addition using BioTek Power Wave XS spectrophotometer (BioTek Instruments, Winooski, VT).

Results revealed that the ethyl acetate fraction prepared from *A. dubia* extract have a potent inhibitory activity on rhAKR1B10 with an IC_{50} 1.57 μg/mL compared to *n*-hexane and *n*-butanol fractions of which IC_{50} values were higher than 10 μg/mL. Epalrestat (2-[(5*Z*)-5-[(*E*)-3-cyclohexyl-2-methylprop-2-enylidene]-4-oxo-2-thioxo-3-thiazolidinyl]acetic acid) was used as a positive control for the experiment, although it is not a specific inhibitor of AKR1B10. Epalrestat, however, is one of the well-known potent inhibitors of AKR1B1 (also called aldose reductase), which has a very similar structure with AKR1B10 [de la Fuente and Manzanaro, 2003]. AKR1B1 is up-regulated in hyperglycemia and reduces glucose to sorbitol, causing secondary diabetic complications [Brownlee, 2001]. Thus, epalrestat is now considered as a positive control for measuring AKR1B10 inhibitory activity. Based on this result, seven major compounds from the ethyl acetate fraction were further isolated, including 3,4-dihydroxybenzoic acid (**1**), quercetin 3-*O*-β-glucose (**2**), 3,4-dicaffeoylquinic acid (3,4-DCQA) (**3**), 3,5-dicaffeoylquinic acid (3,5-DCAQ) (**4**), 4,5-dicaffeoylquinic acid (4,5-DCQA) (**5**), 3,5-DCQA methyl ester (**6**), and 4,5-DCQA methyl ester (**7**) (Fig. 1). The contents of these compounds are presented in Table 1. Results revealed that 3,5-DCQA was the most abundant in both ethanol extract and ethyl acetate fraction. Total contents of **3**, **4**, and **6** (DCQA compounds) were 8.9 and 45.0% in the ethanol extract and ethyl acetate fraction, respectively. Among the isolated compounds, DCQA compounds showed inhibitory activity on rhAKR1B10 in the range of IC_{50} 1.24-2.29 μM, whereas both 3,4-dihydroxybenzoic acid and quercetin 3-*O*-β-glucose showed no inhibitory activity on rhAKR1B10 (Table 2). The inhibitory mode of action was determined by a kinetic analysis using Lineweaver-Burk plots of 1/velocity and 1/concentration of substrate.

Table 2. Inhibitory effects of the isolated compounds from *A. dubia* on rhAKR1B10

Compounds	Concentration (μM)	Inhibition (%)[a]	IC_{50} (μM)
Epalrestat[b]	1.00	44.33±0.85	1.15
3,4-Dihydroxybenzoic acid (**1**)	1.00	5.16±2.41	>10
Quercetin 3-*O*-β-Glc (**2**)	1.00	11.13±6.26	>10
3,4-Dicaffeoylquinic acid (**3**)	1.00	30.44±5.49	2.29
3,5-Dicaffeoylquinic acid (**4**)	1.00	38.90±2.05	1.54
4,5-Dicaffeoylquinic acid (**5**)	1.00	49.15±2.13	1.24
3,5-DCQA methyl ester (**6**)	1.00	37.13±3.99	1.67
4,5-DCQA methyl ester (**7**)	1.00	32.85±1.91	1.96

[a]Data are presented as means±SD, n=3.
[b]Positive control.

Results revealed that all DCQAs and DCQA methyl esters show uncompetitive inhibition against rhAKR1B10 such as epalrestat [Song *et al.*, 2010], indicating that they were not able to specifically bind the substrate or NADPH-binding region of rhAKR1B10 (Data not shown).

Several studies have reported that 3,5-DCQA, 3,4-DCQA, and 4,5-DCQA have antioxidant and anticancer activities *in vitro* through radical-scavenging activity and antiproliferation activity of cancer cells [Iwai *et al.*, 2004; Kurata *et al.*, 2007]. Since AKR1B10 is a now promising target for cancer therapeutics, results of the present study could support one of the plausible mechanisms for explaining the anticancer effects by DCQAs observed in previous studies.

The AKR1B10 inhibitors such as DCQAs also could be used in combination with daunorubicin, an anticancer drug for treatment of lung cancer. Since AKR1B10 is known to inactivate daunorubicin ((8S,10S)-8-acetyl-10-[(2S,4S,5S,6S)-4-amino-5-hydroxy-6-methyl-oxan-2-yl] oxy-6,8,11-trihydroxy-1-methoxy-9,10-dihydro-7H-tetracene-5,12-dione) by reducing the carbonyl group [Martin *et al.*, 2006], the combinatorial treatment with DCQAs could play a role in preventing inactivation of daunorubicin. Results of the present study suggest that the ethyl acetate fraction and DCQAs from *A. dubia* exert inhibitory effects against AKR1B10. Investigation on the effects of DCQAs in various cancer cell types including A549 lung carcinoma cells with a co-treatment of daunorubicin is ongoing.

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