

Anti-oxidant, anti-inflammatory, and anti-carcinogenic activities of araloside A from *Aralia elata*

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ABSTRACT

The aim of this study was to explore the anti-inflammatory and anti-cancer activities of araloside A. Araloside A had a low antioxidant activity. The decrease of 2,2-Diphenyl-1-picrylhydrazyl radicals was only about 5.2% at 200 mM of araloside A. Additionally, the araloside A (200 mM) showed approximately 11% and 9.2% decrease in NO radical chemical scavenging activity and superoxide dismutase-like activity, respectively. The estimated oxygen radical absorbance capacity and hydroxyl radical absorbance capacity values of araloside A were approximately 119.7 mM trolox equivalent/g and 0.818 mM gallic acid equivalent/g, respectively. Based on cytotoxicity results, LPS-stimulated (Lipopolysaccharide) macrophage cells were treated with 0–500 μM of araloside A, a concentration range that did not reduce the viability of macrophage cells. Araloside A inhibited the production of NO in the macrophages in a concentration-dependent manner. In particular, the 500 mM of araloside A reduced NO production to less than the basal level of NO in macrophage cells. Araloside A showed cytotoxicity against the stomach cancer cell lines, SNU-638 and AGS. Additionally, the melanoma cell line B16-F1 was susceptible to araloside A-mediated cytotoxicity. However, the araloside A did not cause cytotoxicity in the ovary cancer cell line NIH: OVCAR-3. Taken together, our results indicated that the araloside A had the anti-inflammatory activity inhibiting NO production and anti-cancer activity against SNU, AGS cancer cells, and melanoma ovarian cancer cells, in spite of its low antioxidant activity. These results provide the fundamental information for araloside A as an agent against both inflammation and cancer.

INTRODUCTION

The relationship between inflammation and cancer has been recognized for a considerable time but the detailed mechanisms were not understood completely. Chronic inflammatory diseases, autoimmunity, and environmental pollutant/foodborne toxin-causing inflammation stimulate the progress of carcinogenesis (Grivennikov *et al.*, 2010). In addition, the inflammation induces the production of cytokines and the reactive oxygen species/reactive nitrogen intermediates, which cause the initiation of tumor progress through mutation of the cell. Inflammation plays an important role in the pathophysiology of cancers. Inversely, the cancers may cause

or intensify inflammation (Diaz *et al.*, 2015). Inflammation and cancer interact with the progress of their pathogenesis each other. For this reason, inflammation and cancer should be considered together in terms of physiological mechanisms, and drugs that have inhibitory effects on both inflammation and cancer are needed.

Various medicinal plants and foods have both anti-inflammatory and anti-cancer activities. Ginger extract (Habib *et al.*, 2008), mushroom extract and its single compounds (Ma *et al.*, 2013), mulberry extract (Eo *et al.*, 2014), and *Tripterygium wilfordii* (Wong *et al.*, 2012) were reported to have the anti-inflammatory and anti-cancer activities. *Aralia elata* (*A. elata*), a medicinal plant for diabetes, hepatics, and stomachache in Korea, China, and Japan (Hu and Wang, 2009), has been investigated for its anti-oxidant activity, anti-cancer activity (Tomatsu *et al.*, 2003), and anti-inflammatory activity (Lee and Jeong, 2009). Araloside A (saponin B, Chikusetsusaponin IV), isolated from *A. elata*, has the anti-gastric and anti-ulcer

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activities against gastric lesions and ulcer by HCl-ethanol and aspirin, respectively (Lee *et al.*, 2005). However, little is known about the anti-inflammatory and anti-cancer activities of araloside A.

The aim of this study was to explore the anti-inflammatory and anti-cancer activities of araloside A to provide fundamental information for the use of araloside A in treatments of both inflammation and cancer.

MATERIALS AND METHODS

Chemical and reagents

2,2-Diphenyl-1-picrylhydrazyl (DPPH), 2,2'-azino-bis(3-ethylbenzothiazoline-6-sulphonic acid) (ABTS), pyrogallol, sodium nitroprusside, and 2,2'-azobis(2-methylpropanimidin e)-dihydrochloride (AAPH) were obtained from Sigma-Aldrich Inc. (St. Louis, MO). Araloside A [Fig. 1, CAS (Chemical Abstract Service): 7518-22-1, $\geq 98\%$ purity by HPLC (High performance Liquid Chromatography)], which is a Saponin B [Chikusetsusaponin IV, 3β -(4-O- α -L-arabinofuranosyl- β -D-glucopyranuronosyloxy)oleana-12-ene-28-oic acid 28- β -D-glucopyranosyl ester], was obtained from Shanghai Yuanye Bio-Technology, Co. Ltd. (Shanghai, China). Cell culture medium and reagents, such as Dulbecco's modified Eagle medium (DMEM), fetal bovine serum (FBS), penicillin/streptomycin, and trypsin-EDTA (Ethylene Diamine Tetraacetic Acid) were purchased from GIBCO (Invitrogen Inc., Grand Island, NY). Other reagents were used as the first-grade reagents.

Assay for antioxidant activity

DPPH radical scavenging activity

Quenching effect of araloside A against DPPH radical was determined by the following procedure: Araloside A (0.2 ml, methanolic solution) was added to 4 ml of methanol and 0.5 ml of 1 mM DPPH. After mixing vigorously for 15 seconds, the mixture left for the reaction at room temperature for 30 minutes. To analyze the scavenging activity of araloside A for DPPH radical, the absorbance of mixtures was measured on 517 nm using UV-spectrophotometry (Libra S22, Biochrom Ltd., CB4 OFJ, England). Scavenging activity of araloside A for DPPH radical was evaluated through the comparison of absorbance between blank and araloside A.

Reducing capacity

Reducing capacity was analyzed by araloside A-mediated Fe^{3+} reduction (Oyaizu, 1986). Araloside A (1 mg/ml) was mixed with 2.5 ml of phosphate buffer (0.2 M, pH 6.6) and 2.5 ml of 1% $\text{K}_3\text{Fe}(\text{CN})_6$. After the incubation of mixture at 50°C for 20 minutes, the reaction mixture was added by 2.5 ml of trichloroacetic acid (10%) and centrifuged at $2,090 \times g$ for 10 minutes. A supernatant layer (2.5 ml) was mixed with distilled water (2.5 ml) and 0.1% FeCl_3 (0.5 ml). The reduction of Fe^{3+} was determined by the absorbance of the mixture at 700 nm using UV-spectrophotometry (Libra S22, Biochrom Ltd., CB4 OFJ, England).

ABTS radical scavenging activity

Scavenging activity of araloside A against ABTS^+ free radical was measured by a little-modified method of [Thaipong *et al.* \(2006\)](#). Scavenging against the ABTS^+ radical was identified using a decolorization reaction (blue-green color) by araloside A. The solution of 7 mM ABTS in phosphate-buffered saline (2.45 mM, pH 7.4) was prepared as a stock and was reacted for 24 hours at room temperature in the dark place for the generation of ABTS^+ radical. Dark blue-green ABTS^+ radical solution was diluted using distilled water to an absorbance value of $0.70 (\pm 0.02)$ on 732 nm using a spectrophotometer (SpectraMax M2; Molecular Devices Inc., Sunnyvale, CA). ABTS^+ solution was prepared freshly for each assay. Araloside A (10 μl , 100 mM) was added to 190 μl of the ABTS^+ solution and was allowed to react for 30 minutes in the dark. The decrease of absorbance in reactant was determined on 732 nm using spectrophotometer (SpectraMax M2; Molecular Devices Inc.). Trolox was used as a standard for the quantification of ABTS decreases.

Superoxide dismutase like activity

A slight modified method of [Marklund and Marklund \(1974\)](#) was used for the superoxide dismutase (SOD)-like scavenging activity of araloside A. One hundred microliter of araloside A (1 mg/ml), 30 ml of pyrogallol (7.2 mM), and 1 ml of Tris-HCl buffer (50 mM, pH 8.5) were mixed and reacted at room temperature for 10 minutes. After 10 minutes of incubation at room temperature, HCl solution (50 ml, 1 M) was added for stopping the reactions. Absorbance of the reaction mixture was measured using microplate reader (SPARK 10M, Tecan, Grödig, Austria) on 420 nm, and ascorbic acid (0–1 mM) was used as a positive control.

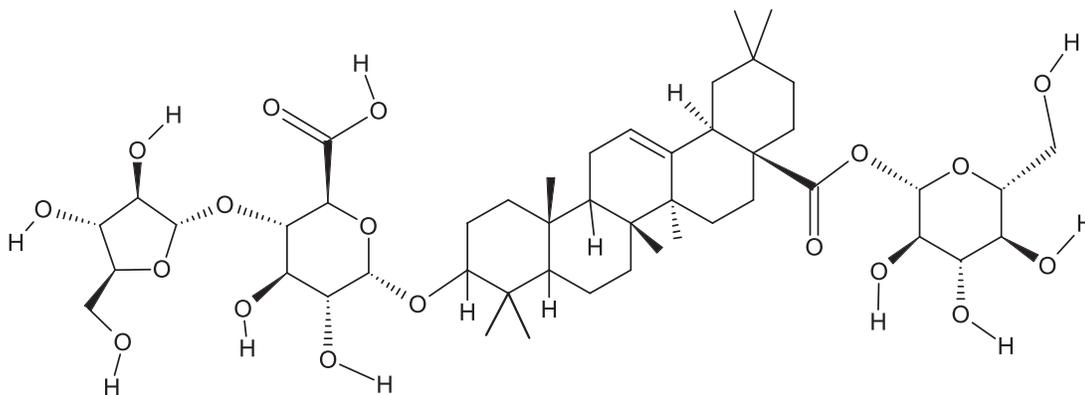


Figure 1. Chemical structure of araloside A.

Chemical scavenging of nitric oxide radical

Chemical scavenging activity of araloside A against nitric oxide radical was analyzed by the following method (Babu *et al.*, 2001). Sodium nitroprusside in the aqueous solution of physiological pH interacts with oxygen and generates NO radical. Araloside A was added to sodium nitroprusside (10 mM in PBS) and reacted at 25°C for 150 minutes. Then, the same amount of reaction mixture and Griess reagent (1% sulfanilamide in 5% phosphoric acid and 0.1% N-1-naphthylethylenediamine dihydrochloride in distilled water) were mixed, and the chromophore formed was measured on 540 nm.

Oxygen radical absorbance capacity and hydroxyl radical absorbance capacity

The oxygen radical absorbance capacity (ORAC) of araloside A was detected by the method of Čiž *et al.* (2010). The ORAC assays monitors the antioxidant scavenging function of araloside A against peroxy radical induced by AAPH. The antioxidant substance inhibits the loss of fluorescence for fluorescein by the peroxy radical. One hundred and seventy microliters of fluorescein solution (60 nM final concentration) and 10 µl of araloside A were added to a well of the microplate (clear bottom, black plate) and were incubated at 37°C for 30 minutes. Then, 20 µl of AAPH (50 mM final concentration) was added to each well rapidly to initiate the reaction. The fluorescence of the mixture was recorded every 5 minutes, and the microplate was automatically shaken before reading by an ELISA (Enzyme-linked Immunosorbent Assay) plate reader (Spark 10M, Tecan, Grodig, Austria). The final ORAC values were calculated by a regression equation between the standard antioxidant trolox concentration and the net area under the curve (AUC). The net AUC corresponding to araloside A was calculated by subtracting the AUC corresponding to the blank. ORAC values were expressed as mg of trolox equivalents (TE)/g dry weight (DW) of araloside A.

The hydroxyl radical absorbance capacity (HORAC) measures the metal-chelating and protection ability activities of araloside A against hydroxyl radicals (Lee and Lee, 2014). Fluorescein 170 µl (60 nM, final concentration) and 10 µl of araloside A were mixed for 10 minutes in an ELISA plate reader (Spark 10M, Tecan, Grodig, Austria) at 37°C. Then, 10 µl of H₂O₂ (27.5 mM, final concentration) and 10 µl of Co(II) (15.7 mg of CoF₂·4H₂O and 20 mg of picolinic acid in 20 ml of distilled water) were added. Fluorescence of each well in a microplate was recorded every 5 minutes for 1 hour with a shaking. Gallic acid was used for plotting of a standard curve, and the AUC values were calculated in the same manner as for the ORAC assay. The HORAC of araloside A was expressed as milligram of gallic acid equivalents (GAEs)/g DW of araloside A.

Cell lines and culture condition

Macrophage cells (RAW 264.7) and melanoma B16-F1 [American Type Culture Collection (ATCC) CRL-6323, skin cancer cell line] were purchased from Korean Cell Line Bank (KCLB) and ATCC (ATCC, Rockville, MD), respectively, and was cultured using DMEM with 10% FBS and penicillin/streptomycin solution (finally, 1 units/ml and 1 µg/ml). SNU-638, AGE cell line (stomach cancer cell line), and adenocarcinoma (ovary cancer cell line, NIH:

OVCAR-3) were obtained from KCLB, and was cultured using RPMI-1640 (Rosewell Park Memorial Institute) medium containing 10% FBS and penicillin/streptomycin (finally, 1 units/ml and 1 µg/ml). Cells were cultured in 5% CO₂ humidified incubator at 37°C.

Cell viability assay

Cell viability of macrophage cell, melanoma B16-F1, AGS cell, and adenocarcinoma by araloside A was measured by MTT (Methylthiazolyldiphenyl-tetrazolium bromide) assay. Cells were cultured in 96-well culture plate (Corning Inc., USA) at 5 × 10⁴ cells/well for 24 hours. After araloside A was added to each well of the 96-well culture plate, the cells were incubated again for 24 hours. MTT solution (0.5 mg/ml, final concentration) was added to all wells of the culture plate, and the cells were incubated for 4 hours at 37°C. After discarding all medium from the plates, 100 µl of dimethyl sulfoxide was added to each well for dissolution of formazan formed in cells. MTT formazan was detected by a UV-spectrophotometric plate reader (Spark 10M, Tecan, Grodig, Austria) on 540 nm. Viability of cells was defined as the absorbance ratio (expressed as a percentage) of treated cells to untreated cells.

Determination of NO production from LPS-induced macrophage cells

Macrophage cell was cultured in 96-well culture plate at 5 × 10⁴ cells/well at 37°C for 24 hours. LPS (1 mg/ml, final concentration) was added to each well for the stimulation of NO production, and then a given concentration of araloside A was added to the wells in the culture plate. After 24 hours of incubation, the induced NO in macrophage cells was determined quantitatively using the Griess reaction. NG-monomethyl-L-arginine monoacetate (L-NMMA, 10 mM) was used as a positive control for the inhibition of NO production in macrophage cells (Sutherland *et al.*, 2001).

Statistical analysis

All experiments were performed at least triplicate and were expressed as a mean ± standard deviation. Data were analyzed statistically using one-way analysis of variance and Dunnett's multiple comparison for individual comparisons. Results were considered statistically significant when *p*-values were below than 0.05.

RESULTS AND DISCUSSION

Antioxidant activity of araloside A

The antioxidant activity of araloside A was evaluated using DPPH/ABTS/NO radical scavenging activity, reducing capacity, and ORAC/HORAC assay (Table 1). Araloside A was found to have a low antioxidant activity. The DPPH radical scavenging activity of araloside A increased in a treatment concentration-dependent manner although the decrease of DPPH radicals was only about 5.2% at 200 mM of araloside A. Additionally, the araloside A (200 mM) showed approximately 11% and 9.2% decrease, as compared to the control, in NO radical chemical scavenging activity and SOD-like activity, respectively. The estimated ORAC and HORAC values of araloside A were approximately 119.7 mM TE/g and 0.818 mM GAE/g, respectively. Araloside A had no reducing capacity or ABTS radical chemical scavenging activity.

Table 1. Antioxidant activity of araloside A.

Antioxidant assay	Araloside A (μM)			
	0	50	100	200
DPPH radical scavenging activity ¹	100.2 \pm 2.65 ^a	99.9 \pm 5.75 ^a	97.7 \pm 0.07 ^a	94.8 \pm 3.10 ^a
Reducing capacity	ND ⁶	ND	ND	ND
ABTS radical scavenging activity	ND	ND	ND	ND
NO radical scavenging activity ²	100.0 \pm 1.06 ^a	88.0 \pm 1.65 ^b	88.8 \pm 1.59 ^b	89.0 \pm 0.26 ^b
SOD-like activity ³	100.0 \pm 0.99 ^a	92.2 \pm 1.76 ^b	89.7 \pm 0.81 ^c	90.8 \pm 1.10 ^{b,c}
ORAC ⁴	119.7 \pm 9.44 mM TE/g dw			
HORAC ⁵	0.818 \pm 0.04 mM GAE/g dw			

All values are %control, except of ORAC and HORAC. ¹Concentration of DPPH radical is 100 μM . ²NO radical is 10 mM SNP (sodium nitroprusside). ³Pyrogallol (0.182 mM) was used for SOD-like activity. ⁴ORAC: oxygen radical absorbance capacity. ⁵HORAC: hydroxyl radical absorbance capacity. ⁶ND: Not detected. Values followed by the different letter in the same column are significantly different ($p < 0.05$).

This study is the first report to describe the low level of antioxidant activity for araloside A. Generally, the compounds with physiological activities such as anti-inflammation and anti-cancer tend to have potent anti-oxidative activities (Reuter *et al.*, 2010). Although a potent antioxidant activity in extracts or compounds is expected to be associated with their significant anti-inflammatory and anti-cancer activities, it does not necessarily guarantee this characteristic. Cai *et al.* (2004) reported that among 112 Chinese medical herbs with anti-cancer activity, approximately 43.8% of herbs had a weak antioxidant activity and only 18.7% of herbs had a high anti-oxidant activity. Additionally, the flavonoid gnapthaliin and pinocembrin had a much lower DPPH radical scavenging activity and superoxide anion scavenging activity compared to tiliroside. However, the anti-inflammatory activities of gnapthaliin and pinocembrin were similar or slightly better than those of tiliroside for mouse paw edema induced by phospholipase A₂ or serotonin, for ear edema induced by TPA-induced ear edema, and for sheep red blood cell-induced delayed hypersensitivity (Sala *et al.*, 2003).

Inhibition of NO production in LPS-stimulated macrophage cells by araloside A

The cytotoxicity of araloside A against macrophage cells was investigated in a preliminary study by determining the level of inhibition of NO production in LPS-stimulated macrophage cells; NO production is one of the major biomarkers for inflammatory activity. No cytotoxicity against macrophage cells was found in 0–500 μM of araloside A; however, 1,000 μM of araloside A showed approximately 17% cytotoxicity (Fig. 2A). Based on this result, we selected the 0–500 μM concentration range of araloside A for subsequent experiments, as this would not affect the viability of the macrophage cells.

NO production in macrophage cells was stimulated significantly from 0.8 to 46.3 μM by addition of LPS (Fig. 2B). NG-methyl-L-arginine (NMMA, 10 μM), an inhibitor for inducible nitric oxide synthase (iNOS), suppressed NO production to 16.3 μM (35.2%, % control) in LPS-stimulated macrophage cells. Araloside A (25–500 mM) was added to LPS-stimulated macrophage cells and found to inhibit production of NO in a concentration-dependent manner. Treatment with 50 and 100 mM of araloside A resulted in 2.8% and 11.7% inhibition of NO production, respectively. Especially, 500 mM of araloside A inhibited significantly NO production to less than basal level of NO in macrophage cells.

Anti-inflammatory suppression of NO production in LPS-stimulated macrophage cells by saponins was reported by several researchers. Saponins from *Tacca vietnamensis* and *Panax ginseng* inhibited significantly NO production, expression of related enzymes, and production of various cytokines, which are involved in the anti-inflammatory process (Jang *et al.*, 2016). The oleanolic acid 3-O-beta-D-glucopyranosyl(1 \rightarrow 3)-alpha-L-rham-nopyranosyl(1 \rightarrow 2)-alpha-L-arabinopyranoside, a triterpenoid saponin in *A. elata*, has been shown to inhibit LPS-induced NO production by down-regulating production of the NF- κ B protein complex in macrophage cells (Suh *et al.*, 2007). Based on these result, we suggest that the anti-inflammatory activity of araloside A (saponin B) acts through inhibition of NO production in LPS-induced macrophage cells.

Cytotoxicity of araloside A against cancer cell lines

Cell viability of various cancer cell lines by treatment of araloside A was investigated, as shown in Figure 3. Araloside A had a cytotoxic effect against the stomach cancer cell lines SNU-638 and AGS. The SNU cells showed the dose-related cell death with approximately 62% and 92% of cell death by the addition of 100 and 200 mM araloside A, respectively. No cytotoxicity was observed in AGS cells after addition of 50 mM araloside A, but 13% and 92% cell death was shown by the treatment of 100 and 200 mM araloside A, respectively. Additionally, melanoma had a susceptible cytotoxicity in 100–200 mM of araloside A and showed approximately 96% of cytotoxicity in 200 mM of araloside A. By contrast, the ovary cancer cell line NIH: OVCAR-3 did not show any cytotoxicity after treatment with 0–200 mM of araloside A. Taken together, araloside A varied in its toxicity depending on cancer cell lines; especially had a potent cytotoxicity against stomach cancer cell lines (SNU and AGS cells).

Saponins, isolated from *A. elata*, showed anti-cancer activity against human leukemia cancer cells (HL60), human lung cancer cells (A549), and human prostatic cancer cells (DU145) (Zhang *et al.*, 2012). The anticancer activity of araloside A in this study was consistent with the previous reports. Several compounds from herbal extracts had both anti-cancer and anti-inflammatory activities, and the related mechanisms were elucidated. Ergosterol peroxide/trametenic acid from *Inonotus obliquus* suppressed the activity of NF- κ B and production of NO significantly and provided the significant

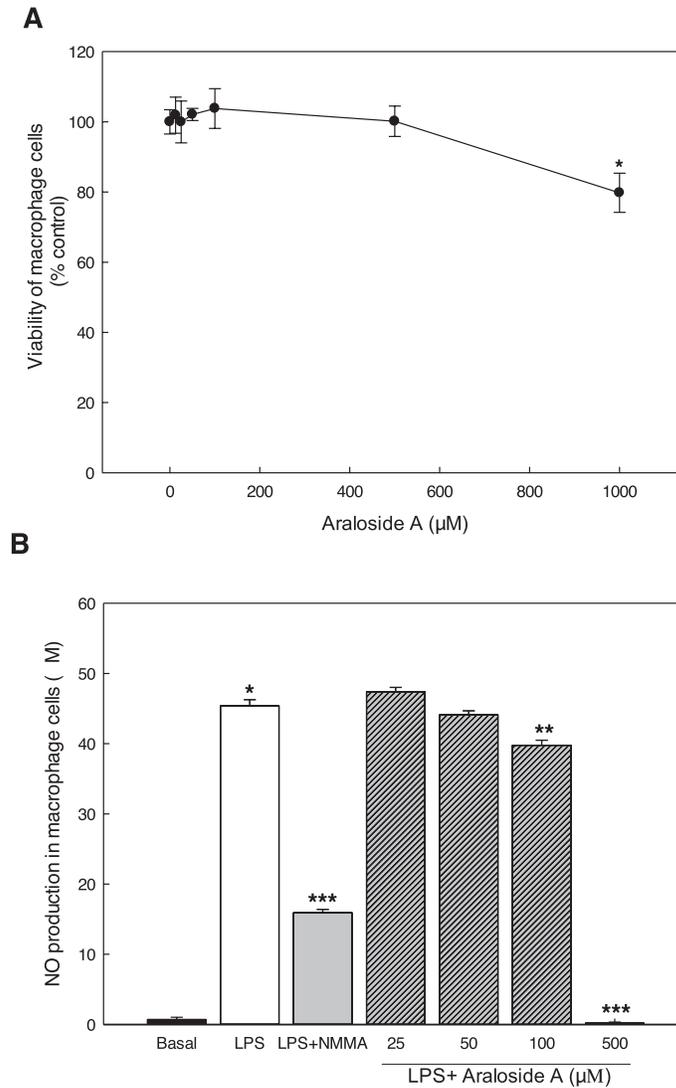


Figure 2. Cell viability and inhibition of NO production from LPS-induced macrophage cells by araloside A. Viability of macrophage cells by araloside A. * $p < 0.001$, compared to the control; B: * $p < 0.001$, compared to the basal; ** $p < 0.05$ and *** $p < 0.001$, compared to the LPS-treated group.

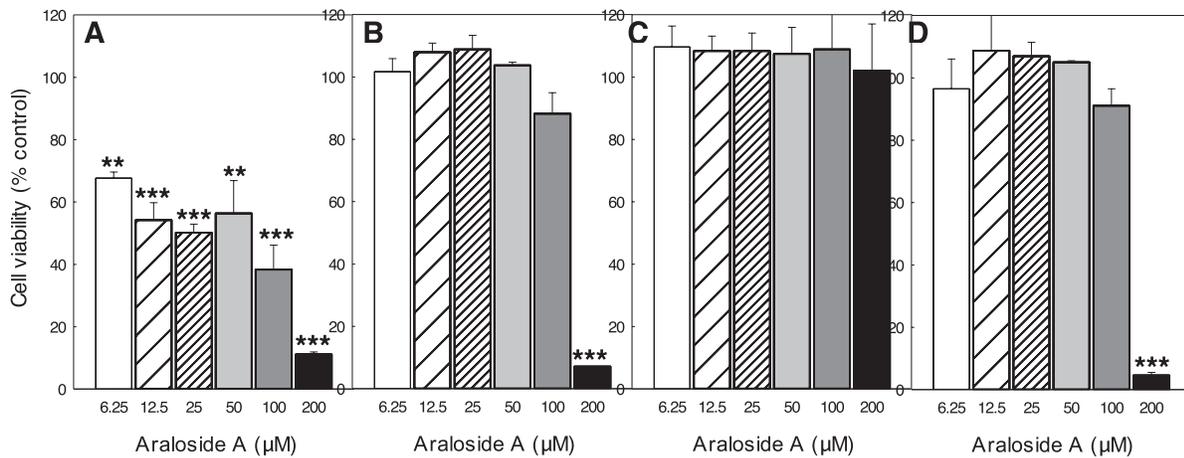


Figure 3. Anti-carcinogenic activity of araloside A. (A) SNU: stomach cancer cell (control = 99.99% ± 15.24%), (B) AGS: stomach cancer cell (control = 100% ± 9.15%), (C) Melanocyte: skin cancer cell (control = 100.04% ± 8.46%), and (D) SK-OV-3: ovary cancer cell (control = 100.28% ± 9.90%), ** $p < 0.005$ and *** $p < 0.001$, compared to the control.

cytotoxicity against the breast cancer cells (Ma *et al.*, 2013). Thus, many single compounds had both anti-inflammatory and anti-cancer activities, and it has been proved scientifically in an animal study, as well as cellular level.

Cancers are associated with inflammation, and the expression of inflammatory genes has an inverse correlation with the progress of cancers and their prognosis. Production of NO was reported to contribute to carcinogenesis, and the uncontrolled overproduction of NO caused the improved duplication of oncogenes and oxidative damage in DNA. It has been well known that the pro-inflammatory mediators contribute to carcinogenesis and progress of cancers. NF- κ B, a pro-inflammatory cytokine, activates the oncogenes and surviving genes, such as cyclin D1 and *c-myc* (Zhu *et al.*, 2001). Actually, NF- κ B was active constitutively in clinical samples of the patients with multiple myeloma, lung cancer, and pancreatic cancer (Tang *et al.*, 2006; Dhillon *et al.*, 2008). Patients with colitis infection-caused inflammation have a high risk for the progression of colon cancers (Itzkowitz and Yio, 2004), and chronic inflammation due to *Helicobacter pylori* makes patients vulnerable to some cancers (Peter and Beglinger, 2007). Additionally, the anti-inflammatory agents, such as nonsteroidal anti-inflammatory drugs, had a role as therapeutic agents for cancers (Coussens and Werb, 2002). These various reports indicated a clear relationship between anti-inflammatory activity, including the suppression of NO production, and cytotoxicity against cancer cell lines. It will be necessary to elucidate the more detailed mechanisms between anti-inflammatory and anti-cancer mechanisms.

CONCLUSION

Araloside A had anti-inflammatory activity inhibiting NO production, and anti-cancer activity against SNU, AGS cancer cells, and ovarian cancer cells. This study demonstrated the potential health-enhancing activity of araloside A due to its inhibition of both inflammation and cancer in spite of its low anti-oxidative activity.

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CONFLICT OF INTEREST

There is no conflict of interest.

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