In Vitro Antitumor Activity of Diterpenes from *Aralia cordata*

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(Received September 29, 1995)

Key words : *Aralia cordata*, antitumor, (ent)-*pimara*-8(14),15-dien-19-oic acid, (ent)-*kaur*-16-en-19-oic acid.

The medicinal herb, *Aralia cordata* of Araliaceae family is widely spread in northeast Asian countries, is currently rare in wild but commonly cultivated and available commercially. In folk medicine, the roots of this species is called Dokwhal (獨活) and has been used frequently as anti-rheumatics or antipyretics. Many constituents including two famous isomeric diterpenes, (ent)-*pimara*-8(14),15-dien-19-oic acid (**I**, PA) and (ent)-*kaur*-16-en-19-oic acid (**II**, KA, Fig. 1.) were reported decades ago (Shibata *et al.*, 1967). Moreover, various kinds of biological activity of this herb has been evaluated earlier such as anti-inflammatory (Han *et al.*, 1985), analgesic (Okuyama *et al.*, 1991), sedative (Wang *et al.*, 1988), antihepatotoxic (Yang *et al.*, 1986), antifungal (Picman *et al.*, 1990) and antithrombotic activities (Han *et al.*, 1986). Interestingly, most of them mentioned that the biological activity of *Aralia cordata* that they had estimated was predominantly attributed to two major diterpene components, PA(**I**) and KA(**II**).

Ongoing search for potent antitumor substances from Korean medicinal plants, we recently found that the methanol extracts of the roots of *Aralia cordata* exhibited an inhibitory effect on the proliferation of cultured human tumor cells, *in vitro*. Hence, the repeated chromatographic separation of the ether soluble acidic portion of the methanol extracts monitored by the cytotoxic effects against human tumor cells has been carried out and finally resulted in the isolation of **I** and **II** as active principles. Both the sodium salts of **I** and **II** were found to exhibit a moderate inhibition upon the proliferation of five kinds of cultured human tumor cells, *i.e.*, A549 (non small cell lung adenocarcinoma), SK-OV-3 (ovarian), SK-MEL-2 (skin melanoma), XF498 (CNS) and HCT15(colon) *in vitro* (Table I) (Detailed experimental procedures are in reference, Ryu *et al.*, 1992). These results were well accorded with the report that KA (**II**), isolated from Annona species, was found to show some lethal effects on brine shrimp (Hui *et al.*, 1989 and 1991). Many cytotoxic or antitumoral diterpenes in diverse categories such as in quassinoid, triptolide, abietane and taxane classes had been so far reported. Besides, intensive investigations on the antitumor property of kaurane-type diterpenes have been carried out (Lien *et al.*, and references therein, 1984), which are usually called *Isodon* diterpenes and differ from **I** or **II** by the lack of carboxyl group and the additional substitution of hydroxyl or epoxy groups on the skeleton. However, this is the first report on the assessment of antiproliferative effects of **I** and **II** especially against cultured human tumor cell lines, *in vitro*.

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Table I. Inhibition of tumor cell proliferation by diterpenes from *Aralia cordata* (Araliaceae) *in vitro*.

COMPOUND	ED_{50} (μg/ml)*				
	A549	SK-OV-3	SK-MEL-2	XF498	HCT15
I	12.8	16.8	14.0	12.8	12.6
II	8.9	13.0	12.8	12.6	9.3
Adriamycin	0.1	0.2	0.1	0.2	2.4

*ED_{50} value of compound against each cancer cell line, which was defined as a concentration that caused 50 % inhibition of cell proliferation *in vitro*.

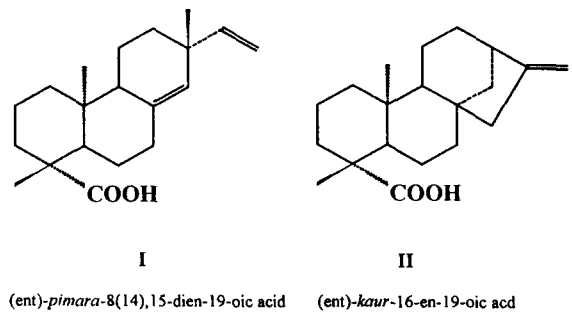

Fig. 1. Two diterpenes from *Aralia cordata*

ACKNOWLEDGEMENT

This work was supported by the grant of "G-7 projects", the special research on the development of new antitumor agents from natural resources, Ministry

of Science and Technology, Korea.

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