Antiproliferative effect of Arctigenin and Arctiin

Shi Yong Ryu[1], Jong Woong Ahn[1], Young Hwa Kang[2] and Byung Hoon Han[2]

[1]Korea Research Institute of Chemical Technology, Taejeon 305-606, Korea and [2]Natural Products Research Institute, Seoul National University, Seoul 110-460, Korea

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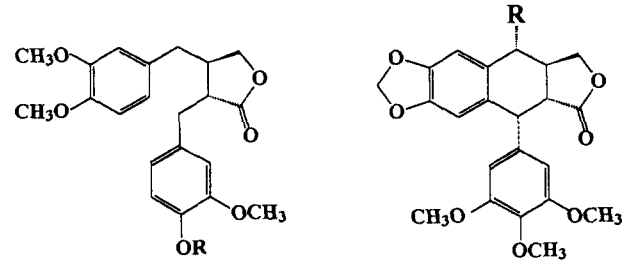
Arctigenin (I) and arctiin (II) are butyrolactone lignans (Fig.1) isolated from the seed of *Arctium lappa* (Compositae) (Han *et al.*, .1994, and more references are therein). These compounds have been reported to show a variety of biological activities such as an antagonistic effect on the PAF receptor (Iwakami *et al.*, 1992), antinephritic activity (Takeda *et al.*, 1990), the calcium antagonistic and antihypertensive effect (Ichikawa *et al.*, 1986) and detoxification effect against amaranth toxicity (Kiriyama *et al.*, 1991). Eich *et al.* reported that arctigenin (I) was found to inhibit strongly the replication of human immunodeficiency virus type 1 (HIV-1; strain HTLV-IIIB) *in vitro* and also inhibit the reverse transcriptase activity of HIV-1 (Eich *et al.*, 1990). Recently, it was reported that both I and II induced differentiation of cultured M1 (mouse myeloid leukemia) cells to phagocyted ones, but inactive towards a human acute promyelocytic leukemia cell line (HL-60) (Umehara *et al.*, 1993). Besides, many natural or synthetic lignans has been reported so far to show antibiotic, antifungal or antitumor activity (Figgitt *et al.*, 1989). In fact, although podophyllotoxin (III), a lignan from *Podophyllum* genus and once regarded as a candidate for a potent antitumor agent, has heen abandoned to be developed by the industrial field due to its extremely high toxicity to human, tremendous efforts were still concentrated on the synthesis of new podophyllotoxin analogues or on the search for new linan compounds to exploit them as antitumor agents. However, to our best knowledge, arctigenin (I) and arctiin (II) have not been reported in relation to the inhibitory effect upon the proliferations of human tumor cells or of microorganisms, even though they might be expected to show such activities due to the structural resemblance with those of well-known antitumor agents, podophyllotoxin (III) or other related lignans (Fig. 1). Herein, we describe results on the estimation of antiproliferative effects of I and II on several microorganisms and on human tumor cells in vitro.

Both I and II were assessed on the antibacterial activity by the agar dilution method against 20 kinds of pathogenic microorganisms, *i.e.*, *Streptococcus pyogenes* 308A, *Streptococcus pyogenes* 77A, *Streptococcus faecium* MD 8b, *Staphylococcus aureus* SG 511, *Staphylococcus aureus* 285, *Staphylococcus aureus* 503, *Escherichia coli* 078, *Escherichia coli* DC 0, *Escherichia coli* DC 2, *Escherichia coli* TEM, *Escherichia coli* 1507E, *Pseudomonas aeruginosa* 9027, *Pseudomonas aeruginosa* 1592E, *Pseudomonas aeruginosa* 1771, *Pseudomonas aeruginosa* 1771M, *Salmonella typhimurium, Klebsiella oxytoca* 1082E, *Klebsiella aerogenes* 1522E, *Enterobacter cloacae* P99 and *Enterobacter cloacae* 1321E. Neither I nor II were found to show significant inhibitory activity upon the growth of any tested microorganisms below



I. (-)-arctigenin, R=-H III. podophyllotoxin, R=-OH
II.(-)-arctiin, R=-Glc IV. desoxypodophyllotoxin, R=-H

Fig. 1. Lignans from *Arctium lappa* (I-II) and *Anthriscus sylvestris* (III-IV)

Table I. Inhibition of *in vitro* tumor cell proliferation by some lignans from plants

COMPOUND	ED_{50} (μg/ml)*				
	A549	SK-OV-3	SK-MEL-2	XF498	HCT15
I	2.8	2.5	1.0	1.2	0.4
II	10.0	5.0	3.5	4.8	0.4
III	2.4×10^{-4}	1.4×10^{-4}	1.7×10^{-4}	2.8×10^{-4}	1.5×10^{-4}
IV	0.3×10^{-4}	1.2×10^{-4}	0.4×10^{-4}	1.8×10^{-4}	0.4×10^{-4}
Adriamycin	0.1	0.2	0.1	0.2	2.4
cisplatin	2.1	1.5	0.8	0.5	0.3

*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*.

Correspondence to: Shi Yong Ryu, Korea Research Institute of Chemical Technology, P.O. Box 107, Yoo Sung, Taejeon 305-606, Korea

the concentration of 200 μg/ml. Whereas, both I and II were found to exhibit a signigicant antiproliferative activity against 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* (Ryu *et al.*, 1992). The potency of them was much lower (ca 10^{-4} times) than that of podophyllotoxin(III) or of desoxyphodophyllotoxin (IV), but as much as that of cisplatin or adriamycin, potent antitumor agents commercially available (Table I).

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