ANTITUMOR ACTIVITY OF FATTY ACIDS PRODUCED BY FUNGI

Sir:

In our screening programme for an antitumor agent using the mouse EHRLICH ascites tumor, it was found that fatty acids extracted from some fungal mycelia showed significant antitumor activity *in vivo*. In primary screening, the acetone extracts of the mycelia of *Penicillium crustosum* IAM 7014, *Pen. tardum* IAM 7206, *Caphalosporium diospyri* and *Sepedonium ampullosporum* showed antitumor activity against EHRLICH ascites carcinoma implanted in mice, strain *ddY*, five weeks of age, weighing approximately 20 g. These four cultures are type cultures of our laboratory, belonging to fungi. The mycelial extracts were fractionated through silica gel column chromatography and the antitumor activity of each fraction was determined *in vivo*. The active principles were eluted from the columns with either hexane or benzene as eluents and obtained as colorless oils by evaporating the solvents *in vacuo*. The active fractions were then purified by repeated preparative thin-layer chromatography and biological and chemical properties were determined.

Table 1. Antitumor activity of fatty acids produced by fungi

Sources	Dose (mg/mouse/day)	Body wt. gain 7 days after implantation (g)	Survival time (days)
Penicillium crustosum	14	4.4	>30
	3.5	5.4	23.5
Penicillium tardum	20	2.1	>30
	50	4.0	>26.5
Sepedonium ampullosporum	20	0.5	>26.5
	5	1.6	>25.5
Cephalosporium diospyri	16	0.7	27
	4	4.0	>25.5
Control	—	8.2	15.7

Mice strain *ddY*, 5 weeks of age weighing 18~22 g were used in this experiment. Two mice were used in each dose. The fatty acids were insoluble in water so they were used as homogenized suspensions in distilled water by adding Tween-80 for dispersion. Treatment was initiated 24 hours after intraperitoneal implantation of 2×10^6 EHRLICH ascites tumor cells, the fatty acids being given intraperitoneally once daily for 5 consecutive days in a total volume of 0.2 ml. Control mice that had been implanted with the tumor received an equal number of injections of the diluent.

The antitumor activity of materials from these four cultures is demonstrated in Table 1. All of these preparations were relatively non-toxic to mice, since at the higher doses tested, significant loss of body weight and any toxic symptoms were not observed. It was necessary to administer at doses of 3.5~20 mg per mouse per day for treatment of the tumor. The dose is high as compared with other antitumor agents. At the two doses shown in Table 1, significant antitumor activity was observed; some of the treated mice were completely recovered from the tumor and the rest of them showed prolonged life-span. At a dose of 30 mg per mouse per day the mice died within a few days due to the toxicity.

The active materials that gave a single spot in silica gel thin-layer chromatography showed only end absorptions in ultraviolet absorption spectra; the infrared absorption spectra of them were identical with each other and similar to that of linoleic acid[1]. The nuclear magnetic resonance spectra were also identical, indicating that they were long-chain fatty acids[2]. When the methyl esters of the isolated materials were separated by gas chromatography using a 1,4-butanediol succinate polyester column, the materials were shown to be mixtures consisting of hexadecanoic, octadecaenoic and octadecadienoic acids as major constituents. This was further confirmed by mass spectra in which the parent peaks corresponding to these fatty acid methyl esters were observed.

Studies on the chemistry, antitumor spectrum and mode of action of these antitumor active fatty acids are under way and the details of the results will be reported elsewhere.

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