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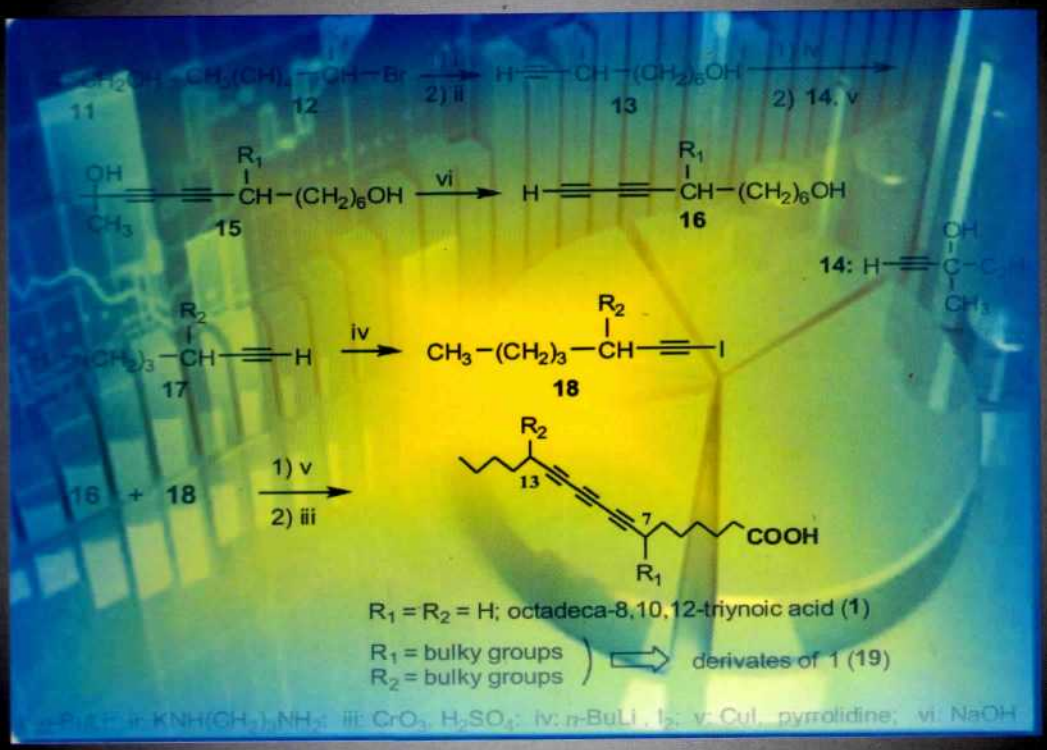
Jurnal Ilmu-ilmu Hayati



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Keterangan gambar cover depan: *Aluryang dipercaya sebagai pathway sintesa kimia asam oktadeka-8,10,12-triunoat, yang memiliki aktivitas antiproliferasi terhadap empat jenis galur sel kanker manusia, sesuai makalah di halaman 343* - H Winarno - Center for the Application of Isotopes and Radiation Technology - Badan Tenaga Atom Nasional.

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      Kramer PJ. 1983. *Plant Water Relationship,* 76. Academic, New York.
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      Hamzah MS dan SA Yusuf. 1995. Pengamatan beberapa aspek biologi sotong buluh *{Sepioteuthis lessoniana)* di sekitar perairan pantai Wokam bagian barat, Kepulauan Aru, Maluku Tenggara. *Prosiding Seminar Nasional Biologi XI,* Ujung Pandang 20-21 Juli 1993. M Hasan, A Mattimu, JG Nelwan dan M Litaay (Penyunting), 769-777. Perhimpunan Biologi Indonesia.
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      Leegood RC and DA Walker. 1993. Chloroplast and Protoplast. In: DO Hall, JMO Scurlock, HR Bohlar Nordenkampf, RC Leegood and SP Long (Eds.). *Photosynthesis and Production in a Changing Environment,* 268-282. Champman and Hall. London.

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DAFTAR ISI

MAKALAH HASIL RISET (ORIGINAL PAPERS)

ANTIPROLIFERATIVE ACTIVITY OF OCTADECA-8,10,12-TRIYNOIC ACID AGAINST HUMAN CANCER CELL LINES'

[Antiproliferasi Asam Oktadeka-8,10,12-triunoat Terhadap Galur Sel Kanker Manusia]

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ABSTRACT

Antiproliferative activity test of **octadeca-8,10,12-triynoic** acid isolated from parasitic plant *Scurrula airopurpurea* (Bl.) Dans, against four kinds of human cancer cell lines, i.e: HeLa (human cervix epitheloid carcinoma), leukemia THP1, (human peripheral blood acute monocyte). carcinoma A549 (human lung carcinoma) and lymphoma HUT78 (human cutaneous T-cell lymphoma) was carried out. The results showed that octadeca-8.10,12-triynoic acid exhibits the antiproliferative activity against four kinds of human cancer cell lines with the $1C_{50}$, value of 0.66. 0.86, 0.99 and 2.36 mg/nil for HeLa. leukemia THP1, lung carcinoma A549, and lymphoma HUT78, respectively, lower than 4 mg/ml. which is the antiproliferative activity threshold for pure isolate or compound.

Keywords: Octadeca-8,10,12-triynoic acid, aniiproliferativc. human cancer cell lines. HeLa, THIM, A549, HUT78

ABSTRAK

Telah dilakukan uji aktivitas **antiproliferasi asam oktadeka-8.10,12-triunoat** yang diisolasi dari benalu ten *Scurrula airopurpurea* (Bl.) Dans, terhadap empat jenis galur sel kanker manusia, yaitu HeLa *{human cervix ephileloid carcinoma),* leukemia THP1 *{human peripheral blood acme monocyte).* karsinoma paru-paru A549 *(human lung carcinoma)* dan limfoma HUT78 *(human cutaneous T-cell lymphoma).* Hasil uji menunjukkan bahwa asam oktadeka-8.10,12-triunoat memiliki aktivitas antiproliferasi terhadap empat jenis galur sel kanker manusia yang diuji dengan nilai IC_{50} adalah 0.66. 0.86. 0.99 dan 2.36 mg/ml berturut-turut untuk HeLa. leukemia THIM. karsinoma paru-paru A549 dan limfoma HUT78. Nilai tersebut lehih rendah dari 4 mg/ml. yang merupakan batas suatu isolat murni atau senyawa dinyatakan memiliki aktivitas antiproleferasi.

Kata kunci: asam oktadeka-8,10,12-triunoat, antiproliferasi, galus sel kanker manusia, HeLa, THP1, A549, HLJT78.

INTRODUCTION

Medical treatment for cancer patients such as radiotherapy and chemotherapy are promoting, but costly. Hence, assessment of bioactive compounds from herbal is an important issue to be conducted.

Tea parasitic plant *Scurrula atropurpurea* (Bl.) Dans. (Loranthaceae) is hemiparasite lives on tea plant *{Thea sinensis).* Some of the Loranthaceous plants have been recognized widely as traditional medicine in the world (Cheng, 1997). In Japan, *Viscum album* L. *van lutescens* MAKINO has been used as traditional medicine to treat lumbago, after childbirth. On the other hand, *Viscum album* L. has been used to treat some diseases in Europe since long time ago. Research on anticancer drugs have become a focus, however, the evidence based on effectiveness are still scant (Cheng, 1997). In Indonesia, the tea parasitic plant infusion has been used as traditional medicine for cancer treatment.

Bioactive compounds isolated from the tea parasitic plant *S. atropurpurea* have been obtained; there are six kinds, namely of C_{18}-fatty acids [(Z)-9-octadecenoic acid, (Z,2)-octadeca-9,12-dienoic acid, (Z,Z,Z)-octadeca-9,12,15-trienoic acid, octadeca-8,10-diynoic acid, (Z)-octadec-12-ene-8,10-diynoic acid, octadeca-8,10,12-triynoic acid], two kinds of xanthines (theobromine and caffeine), two kinds of flavonol glycosides (quercitrin and rutin), a monoterpene glucoside (icariside B,), a lignan glycoside (aviculin), and four kinds of flavanes [(+)-catechin, (-)-epicatechin, (-)-epicatechin-3-O-gallate, and (-)-epigallocatechin-3-O-gallate]. The chemical structures of these bioactive isolated compounds were confirmed, based on the physico-chemical evidences (Ohashi *et at.*, 2003a; Winarno, 2003; Winarno, *et al*,2003).

The assessment of those isolated compounds on the inhibitory effect against MM1 cancer cell invasion was carried out based on the previous method (Akedo *et al.,* 1986), and showed that the C_{18}-trialkynic

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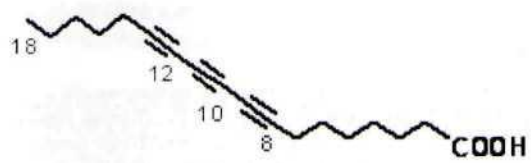
fatty acid, namely octadeca-8,10,12-triynoic acid (1) exhibits the most potent inhibitory activity with an IC_{50} of 2,7 lag'ml (Ohashi *et al.*, 2003a; Winarno, 2003). It was assumed that octadeca-8,10,12-triynoic acid (1) may be the active principal of the tea parasitic plant *Scurrula atropurpurea* which has been used for treatment of cancer in Indonesia.



octadeca-8,10,12-triynoic acid (1)

Figure 1. The Chemical structure of octadeca-8.10,12-triynoic acid isolated from *Scurrula atropurpurea*

Based on these facts, octadeca-8,10.12-triynoic acid (1) was further tested on its antiproliferative activity *in vitro* against human cancer cell lines, namely cervix HeLa, leukemia THP1, lung carcinoma A549 and lymphoma HUT78.

MATERIALS AND METHODS

Materials

Octadeca-8,10,12-triynoic acid (1) was isolated from *S. atropurpurea* with the same method as described in the previous paper (Ohashi *et al.*, 2003a). Human cancer cell lines cervix HeLa (human cervix epitheloid carcinoma), leukemia THP1 (human peripheral blood acute monocyte), carcinoma A549 (human lung carcinoma), and lymphoma HUT78 (human cutaneous T-cell lymphoma) was obtained from Cell Culture Laboratory, Division of Pathology, Faculty ofVeterinary Medicine, Bogor Agricultural University, Bogor. Other materials were Dulbecco's modified Eagle's medium (DMEM/F-12), fetal bovine serum (FBS), 10% of phosphate buffer saline (PBS), dimethyl sulfoxide (DMSO). 0,2% of trypsin. 0,4% tryphan blue, liquid nitrogen.

Bioassay **method**

Cancer cell lines in DMEM/F-12 medium containing 2 x 10" cell/ml was placed into the serocluster 24 wells *plate,* then the sample solution of octadeca-8,10,12-triynoic acid in DMSO was added in 6 various concentrations i.e 0 mg/ml (control), 0.5, 1.0, 2.0,4.0 and 8.0 mg/ml. Six mg/ml of doxorubycin was used as positive control. Each concentration was carried out in triplicates. The plate was then incubated at 37°C for 72 h under 5% CO_2 condition. Ninety ml of cell suspension in every well was pipetted and put into serocluster plate (96 well) and 10 ml of tryphan blue was added and the mixture was homogenized. Furthermore, 10 ml of suspension was put in haemocytometer and the amount of viable cells and death cells were enumerated by microscope. The antiproliferative activity was calculated as the following equation:

[Icancer cells in control]

By making the graph of sample concentration in logarithm (X axes) *versus* probit of % antiproliferative activity (Y axes), the linear regression equation. Y = aX+b is obtained. The inhibition concentration-fifty (IC_{50}) which expresses the ability of the samples to inhibit 50% of cancer cell proliferation is calculated by the substitution of Y by 5 (probit value of 50) to the linear regression equation Y = aX+b. Subsequently, IC_{50} value= antilogarithm of X {= antilogarithm of (5-b)/a} can be determined.

RESULTS

Table 1 shows antiproliferative activity against human cancer cell lines of cervix HeLa, leukemia THP1, lung carcinoma A549, and lymphoma HUT78.

The inhibition concentration-fifty (IC_{50}) expresseses the ability of the samples to inhibit 50% of cancer cell proliferation calculated by the substitution of Y by 5 to the each linear regression curve. Y=aX+b as shown in Fig. 2. The antilogaritmic of obtained X was the IC_{50} value. The calculated IC_{50} values were 0.66,0.86. 0.99 and 2.36 mg/ml respectively, for HeLa, leukemia THP 1, lung carcinoma A549 and lymphoma HUT78, as in Table 1. This results supported the previous inhibitory activiy test on MM1 cancer cell invasion (IC_{50} 2,7µg/ml).

Table 1. Antiproliferative activity of octadeca-8,10,12-triynoic acid (1) against cervix HeLa, leukemia THP1, lung carcinoma A549, and lymphoma HUT78

No	Sample	Antiproliferative activity (%)*			
		Cervix HeLa	Leukemia THP1	Lung Carcinoma A549	Lymphoma HUT78
1	OTA, 0 µg/ml (Negative Control)	00.00	00.00	00.00	00.00
2	Doxorubicin 6.0 µg/ml (Positive Control)	70.32	72.31	78.83	75.97
3	OTA, 0.5 µg/ml	45.31	38.46	35.29	16.46
4	OTA, 1.0 µg/ml	60.94	53.85	47.06	27.85
5	OTA, 2.0 µg/ml	76.56	66.15	69.41	48.10
6	OTA, 4.0 µg/ml	87,50	81.54	80.00	63.29
7	OTA, 8.0 µg/ml	96,88	89.23	88.24	77.22
8	IC_{50} (µg/ml)	0.66	0.86	0.99	2.36

OTA = octadeca-8,10,12-triynoic acid (1)
(%)* = average from three experiments

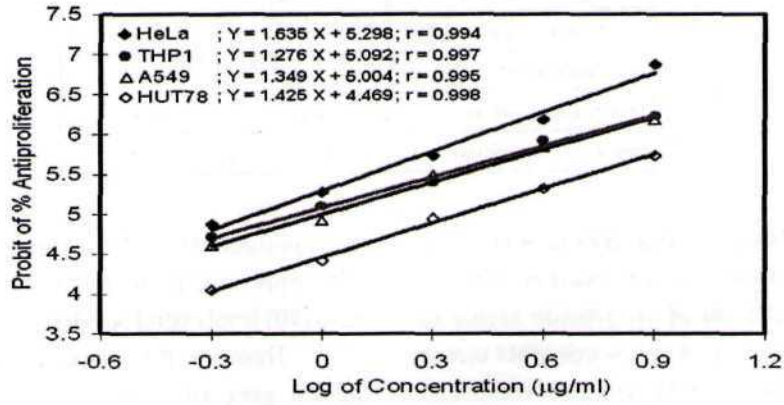


Figure 2. The regression curve of antiproliferative activity *versus* concentration of octadeca-8,10,12-triynoic acid (1) against human cancer cell lines HeLa, THP1, A549, and HUT78

DISCUSSION

Octadeca-8,10,12-triynoic acid (1) exhibited high antiproliferative activity against human cancer cell lines of HeLa, leukemia THP1, lung carcinoma A549 and lymphoma HUT-78. Calculation of IC_{50} value based on linear regression curve (Fig. 2) with the linearity r > 0.99 revealed that the IC_{50} values were 0.66,0.86,0.99 and 2.36 mg/ml respectively, for HeLa, leukemia THP1, lung carcinoma A549 and lymphoma HUT78. The bioactive compound exhibites a potent anticancer at an IC_{50} d" 4.0 µg/ml on antiproliferative activity test against cancer cell line *in vitro* (Swahson and Pezzuto, 1990). This shows that, octadeca-8,10,12-triynoic acid (1) bioactive compound isolated from tea parasitic plant *S. atropurpurea* exhibited antiproliferative activity towards four kinds of human cancer cell lines in this experiment, especially toward cervix HeLa, leukemia THP1 and lung carcinoma A549 with IC_{50} < 1.00 mg/ml. These results confirmed the previous study by Ohashi *et al.* (2003a) that octadeca-8,10,12-triynoic acid (1) might be the active compound of the tea parasitic plant *S. atropurpurea* having anti-carcinogenicity. As described in their paper, the bioactivities of octadeca-8,10,12-triynoic acid (1) might be due to the amount of unsaturation of fatty acid and the position of the triple bonds of C_{18}-alkynic fatty acid in the structure.

Table 2. Comparison of inhibitory activity of saturated and unsaturated fatty acids on MMl cancer cell invasion at concentration of 10 µg/ml (Ohashi *et al.*, 2003a; Ohashi *et al.*, 2003b; Winarno, 2003)

Entry	Chemical Name	Amount of unsaturation of fatty acids	% inhibitory activity
Number of C atom = 18			
1	octadeca-8,10,12-triynoic acid (1)	6	99.4
2	(Z)-12-octadecene-8,10-diynoic acid (2)	5	89.8
3	octadeca-8,10-diynoic acid (3)	4	61.1
Number of C atom = 16			
4	hexadeca-8,10,12-triynoic acid (4)	6	98.7
5	hexadeca-8,10-diynoic acid (5)	4	85.6
6	hexadec-8-ynoic acid (6)	2	82.4
7	palmitoleic acid (7)	1	49.7
8	palmitic acid (8)	0	46.8

Table 3. Comparison of inhibitory activity of triple bonds position in alkynic fatty acids towards MMl cancer cell invasion at concentration of 10 µg/ml (Ohashi *et al.*, 2003 b; Winarno, 2003)

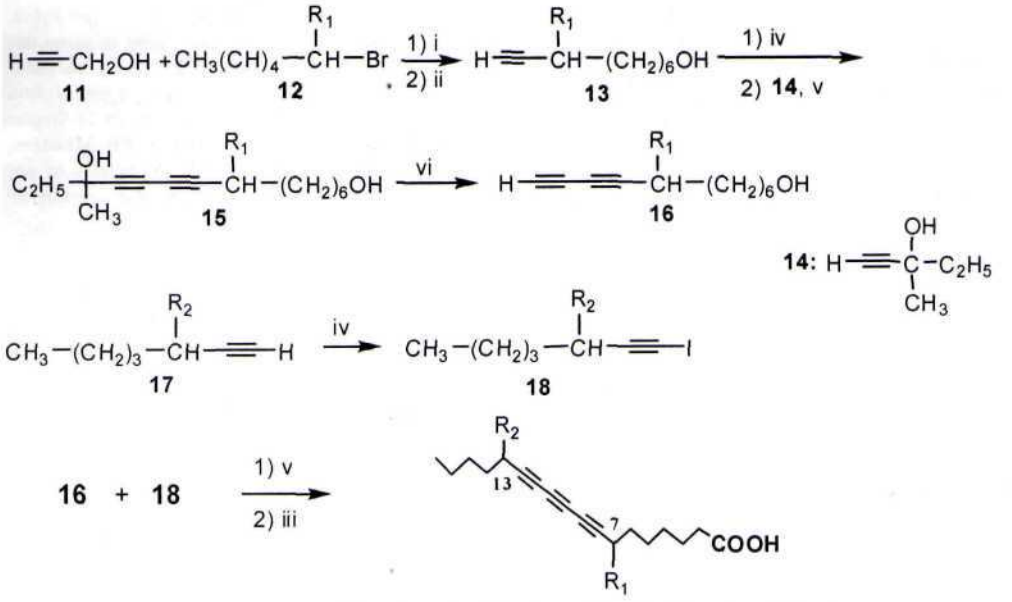
Entry	Chemical Name	triple bond position	% inhibitory activity
Number of triple bond = 3			
1	hexadeca-8,10,12-triynoic acid (4)	C-8,10,12	98.7
2	hexadeca-6,80,10-triynoic acid (9)	C-6,8,10	95.7
Number of triple bond = 1			
3	hexadec-8-ynoic acid (6)	C-8	82.4
4	hexadec-10-ynoic acid (10)	C-10	77.2

As seen in Table 2, it should be noted that the rise in the amount of unsaturation functions with the same amount of C atom of fatty acids seems to strengthen the inhibitory activity towards MM 1 cancer cell invasion. Hence, inhibitory activity of compound 3 (amount of unsaturation = 4) < compound 2 (amount of unsaturation = 5) < compound 1 (amount of unsaturation = 6), then inhibitory activity inhibitory activity of compound 8 (amount of unsaturation = 0) < compound 7 (amount of unsaturation = 1) < compound 6 (amount of unsaturation = 2), inhibitory activity of compound 5 (amount of unsaturation = 4) < compound 4 (amount of unsaturation = 6). The more the unsaturated fatty acid available, the higher activity towards MMl cancer cell invasion.

Subsequently, the position of triple bond which starts at C-8 shows more inhibitory activity towards MMl cancer cell invasion at the same concentration than others (Table 3). The inhibitory activity of hexadeca-8,10,12-triynoic acid (4) (triple bond position at C-8,10,12) > hexadeca-6,80,10-triynoic acid (9) (triple bond position at C-6,8,10), then hexadec-8-ynoic acid (6) (triple bond position at C-8) > hexadec-10-ynoic acid (10) (triple bond position at C-10).

However, the characteristic of trialkynic fatty acid is generally unstable on exposure, octadeca-8,10,12-triynoic acid also unstable, immediately undergo deterioration, change from white powder to blueist-violet gel within few minute. Hence, it make the structure and function group modifications of this isolated compound are needed for developing a better stability. Octadeca-8,10,12-triynoic acid (1) can be synthesized from propargyl alcohol (11), bromohexane (12), and 1 -heptyne (15) based on the previous studies (Zeni *et al.*, 2001, Ohashi *et al*, 2003b, Winarno, 2003) as described in Sheme 1.

By substituting R_1, and $R_2$with bulky groups, the derivates of octadeca-8,10,12-triynoic acid (1) substituted at positions 7 and 13 can be synthesized (19), making the triple bonds at positions 8 and 12 will be hindered, it suggest the compound more stable.



Sheme 1. Plausible chemical synthesis ofoctadeca-8,10,12-triynoicacid (l)and its derivates

CONCLUSSION

Octadeca-8,10,12-triynoic acid (1) isolated from *Scurrula atropurpurea* exhibited antiproliferative activity against four kinds of human cancer cell lines i.e.: human epitheloid cervic carcinoma HeLa (IC_{50} = 0,66 mg/ml), human peripheral blood leukemia acute monocyte THP1 (IC_{50}= 0,86 mg/ml), human lung carcinoma A549 (IC_{50} = 0,99 mg/ml), and human cutaneous T-cell lymphoma HUT78 (IC_{50} = 2,36 mg/ml). Taken together, the bioactive compound has a potent anticancer activity and further examinations such as *in vivo* assay is needed to validate the significant results. Since the compound is unstable, the structure and function group modifications of the compound are needed to develop better stability and activity.

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