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Cytostatic and cytotoxic effects of alkylglycerols (Ecomer)

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C Statistical Analysis
D Data Interpretation
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Summary

Background: Shark liver oil, with a standardized concentration of alkylglycerols and their methoxy-derivates, has been widely used in Scandinavian countries as complementary medicine in the treatment of different forms of cancer. The aim of our study was to verify the hypothesized antiproliferative effect of alkylglycerols in different human cancer cell lines.

Material/Methods: The plating efficiency method was used to assay the effect of alkylglycerols on the plating efficiency of human ovarian carcinoma (OVP-10), mammary carcinoma (MCF-7), and prostate cancer (DU-145, PC-3 and PCa-2b) cell lines. Tumor colonies containing more than 20 cells were scored as positive. Flow cytometry was applied to identify necrotic vs. apoptotic mode of cell death. The cells were exposed to Ecomer® shark liver oil containing 20% alkylglycerols and 3% methoxyderivates in a dose of 0.1 mg/ml, up to a concentration corresponding to LD-50. Apoptotic and necrotic cells were stained with Anexin V and propidium iodine respectively.

Results: The prostate cells from DU-145, PC-3 and PCa-2B showed a dramatic reduction in the colony number even after relatively small doses of 0.5 and 0.1 mg/ml medium. Flow cytomery showed an increased percentage of apoptotic cells of ovarian and prostate carcinoma, while mammary carcinoma cells showed predominantly necrotic cells after exposure to Ecomer.

Conclusions: The alkylglycerols and their methoxyderivates present in Ecomer® shark liver oil showed a clear apoptotic/necrotic effect on human prostate and mammary carcinoma cell lines.

key words: **alkylglycerols • methoxyalkylglycerols • prostate cell lines • ovary cell lines • mammary cell lines**

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BACKGROUND

Shark liver oil is an ancient remedy among the fishermen who live along the west coast of Norway and Sweden. In addition to its use for the treatment of general debility, it has historically had several specific applications, such as wound healing and the treatment of irritation of the respiratory and alimentary tracts. Of particular interest, this oil was also used in the past to treat what was referred to in those days as 'glandular disease', and nowadays would be called lymphadenopathy. It was not until the early part of this century that biochemists discovered substances in this oil that may account for its traditional uses: namely, the alkylglycerols.

Alkylglycerols are glyceryl ether lipids that are structurally characterized by an ether linkage of a fatty acid attached to the chain length and by the number of double bonds; several derivates of the ether lipid have been identified. The principal alkylglycerols include chimyl (hexadecyl), batyl (octadecyl), and selachyl (octadecenyl) alcohols [1]. A small quantity of alkylglycerols is found in the living cells of most animal tissues, particularly in hematopoietic organs, including bone marrow, spleen, liver, and lymphatic tissues and blood [2]. A much higher content of ether lipids is found in malignant tumors than in normal tissues [3], while the highest content of alkylglycerols has been determined in the liver oil of Greenland sharks, the gray dogfish, and the ratfish [1]. Glyceryl ether lipids are also found in human colostrum, human milk, and sheep's milk. Human milk has been found to contain nearly 10 times more alkylglycerols than cow's milk [4].

The biological effects of alkylglycerol have been demonstrated in both animals and human patients with cancers. The administration of alkylglycerol to animals stimulates hematopoiesis, including erythropoiesis, thrombocytosis, and granulocytosis [5–7]. In one study, treatment with shark liver oil alkylglycerols in uterine cervical cancer patients who were receiving radiation therapy significantly reduced the injuries accompanying radiation toxicity, and resulted in enhanced survival rate and survival time [8]. A number of observations have reported that alkylglycerols and alkyl lysophospholipids significantly activate cytotoxic macrophages, leading to enhanced Fc-receptor-mediated phagocytosis [9], increase humoral immune response, and delay hypersensitivity reaction [10]. Other studies have shown that alkylglycerols inhibit the growth of primary tumors and the metastasis of Lewis lung carcinoma growing in C_{57} B6 mice [11]. More recently, Wagner et al. observed a time- and concentration-dependent development of oxidative stress when sensitive HL-60 cells were exposed to membrane-targeted ether lipids [12]. The mechanism of oxidative stress has also been suggested to explain the observed induction of apoptosis in human leukemic cells [13,14]. Induction of oxidative stress and consecutive apoptosis is also assumed to explain the observed inhibition of L-1 sarcoma-induced angiogenesis by alkylglycerols [15]. In 1970, Brohult et al. [16] were the first to describe a reduced mortality rate in cancer patients given glycerol ethers from Greenland shark liver oil. Boeryd et al. [17] in 1971 reported that a methoxy-substituted derivate of alkylglycerols constituting 3% shark oil is active against tumor growth and metastasis formation.

Brohult et al. reported in 1986 that a comparison of preventively treated and control cases among 4404 patients with uterine cancer revealed a significantly lower five-year mortality in subjects treated with shark lover oil (31.0% vs. 39.6% in the control group) [8]. The best results were obtained in more advanced stages of cancer, confirming the observation by Warne et al. that the production of alkylglycerols by tumor cells increases over time [18]. Since the publications by Brohult, shark liver oil, with its standardized concentration of alkylglycerols and their methoxyderivates, has become popular in Scandinavian countries, and is used as an adjunct in the treatment of different form of cancer. It has been commercialized under the name Ecomer®.

The aim of our study was to examine the antiproliferative effect of Ecomer in different human cancer cell lines.

MATERIAL AND METHODS

Five human tumor cell lines were used:
- ovarian carcinoma: OVP-10;
- mammary carcinoma: MCF-7;
- three different prostate cancer cell lines: DU-145, PC-3, and PCa-2b, which are hormone-independent.

All tumor cell lines were routinely propagated in Minimal Essential Medium (MEM) supplemented with 7% fetal calf serum (FCS) and antibiotics.

The sensitivity of tumor cells to Ecomer was tested for plating efficiency, using a method which can be described briefly as follows: 100 cells in 3 ml of FCS-supplemented medium (MEM) were plated on 3 cm diameter Petri dishes. After 24 hours the medium was replaced with a medium containing Ecomer. The cultures were kept for six days and the cells were then fixed with methanol and stained with Giemsa. Tumor colonies containing more than 20 cells were scored as positive.

The method of scoring tumor colonies following any kind of treatment provides information about the fraction that has survived cytotoxic treatment. Determination of the size of the tumor colony when cytotoxic effects are excluded can show whether the cytostatic effect is involved, as indicated by the reduction in the cancer cell colonies size (results not shown). Flow cytometry was applied to differentiate the necrotic or apoptotic mode of cell death. Ecomer (Natumin Pharma AB, Sandefjord, Norway) shark liver oil containing 20% alkylglycerol and 3% methoxy-derivates was kindly supplied by the producer. The cells studied were exposed to Ecomer for 24 h. The Ecomer dose was an LD50 dose selected on the basis of previous experiments. After the 24 h treatment, cells from the cultures were trypsynized to obtain a single-cell suspension and then stained with Anexin V and propidium iodine (Apoptosis detection kit, Caltag Laboratories) for 20 min in dark-

Table 1. Effect of Ecomer treatment on the plating efficiency of tumor cell lines.

	OVP-10		MCF–7		DU–145		PC–3		PCa–2b	
Control	38.5±9.8	n=20	54.9±10.9	n=15	36.5±16.5	n=26	46.6±11.7	n=20	40.2±9.8	n=15
Ecomer 1.0 mg	31.8±8.7	n=20	11.8±7.3	n=15	0	n=20	0	n=6	0	n=6
Ecomer 0.5 mg	36.4±6.7	n=12	24.1±9.2	n=15	8.2±3.5	n=12	0	n=6	4.6±1.2	n=8
Ecomer 0.1 mg	n.d		n.d.		28.6±10.5	n=12	6.3±2.2	n=10	22.4±8.0	n=8
Ecomer 0.05 mg	n.d.		n.d.		n.d.		12.2±6.1	n=10	n.d.	

Mean ±SD;

n – number of repetitions; nd – non-determined

Table 2. Determination by flow cytometry of the percentage of necrotic and apoptotic cells following treatment with an LD 50 dose of Ecomer.

	Live cells (%)	Necrotic cells	Apoptotic cells
OVP-10 Control	79.9±6.5 n=4	7.1±5.6 n=4	13.0±5.3 n=4
OVP-10 Ecomer	62.3±14.0 n=4	12.8±7.6 n=4	24.9±12.2 n=4
MCF-7 Control	85.2±11.0 n=4	7.8±7.3 n=4	7.0±4.3 n=4
MCF-7 Ecomer	71.8±4.2 n=4	20.8±6.4 n=4	7.4±3.9 n=4
DU-145 Control	87.7±2.3 n=4	1.1±0.3 n=4	11.1±2.0 n=4
DU-145 Ecomer	79.0±1.2 n=4	3.0±2.1 n=4	18.0±1.4 n=4

Mean ±SD;

n – number of repetitions

ness. Following the staining, about 400,000 cells were subjected to cytometry using a FACS VANTAGE device (Becton-Dickinson). The detection of necrotic or apoptotic cells by means of the staining here described is based on the assumption that cells stained with Anexin V represent the population of early apoptotic cells. The necrotic cells are stained with propidium iodite. Cells stained with Anexin and propidium iodite represent the population of late apoptotic cells. Non-stained cells are alive. For simplification, early and late apoptotic cells were regarded as a single group, i.e. apoptotic cells.

Results

The results of the plating efficiency study revealed that Ecomer, even at a dose of 1 mg/ml, did not reduce the number of ovarian carcinoma cells in the colony. The Ecomer-treated colonies were found to be smaller than those that developed from non-treated cells (mean 154.0, SD±94.0 vs. mean 931.0, SD±52.3 um^2 respectively). MCF-7 cells displayed some sensitivity. Conversely, the DU-145, PC-3 and PCa-2b prostate cells sho-0wed a dramatic reduction in the colony number, even after doses of 0.5 and 0.1 mg Ecomer per 1 ml medium. The results are presented in Table 1. The flow cytometry study showed an increased percentage of apoptotic cells in ovarian carcinoma and prostate carcinoma after exposure to Ecomer. Mammary carcinoma cells exposed to Ecomer died predominantly by necrosis. The results of the flow cytometry experiments are shown in Table 2.

Discussion

Ecomer® a commercially available shark liver oil, proved to inhibit proliferation in four out of five tumor cell lines. Among the cell lines studied, the ovarian carcinoma cells (OVP-10) were found to be the least sensitive, mammary carcinoma cells (MCF-7) displayed a moderate sensitivity, whereas all three lines of prostate cancer cells showed a high sensitivity to Ecomer. These findings confirm previously described characteristics of alkyl-ether lipids, in particular their selective effects in inhibiting the proliferation of neoplastic cells, with practically no effects on normal cells [19]. The cytostatic and cytotoxic effects of synthetic ether lipids on a wide range of cancer cells and experimental tumors are well documented, and a number of these compounds have been already registered or are undergoing clinical trials [20–23]. Both synthetic ether lipids and natural alkylglycerols have been found to cause growth inhibition of cancer cells without interacting with cellular DNA. Their effects have been ascribed to a wide range of mechanisms, including inhibition of phosphatidylcholine synthesis [21,24], interruption of mitogenic signaling pathways [25,26], and nutrient starvation [27], all of which are known to induce apoptosis [23,28]. The observed anti-proliferative effect of Ecomer could be either cytostatic or cytotoxic. In the case of the ovarian carcinoma cell line (OVP-10), the Ecomer-treated cells developed smaller colonies and displayed a higher percentage of apoptotic cells, which indicates concomitant cytostatic and apoptotic effects. The remaining cell lines mainly showed a cytotoxic effect. Mammary carcinoma cells, on the other hand, displayed mainly a necrotic mode of death, while DU-145 prostate cancer cells underwent clearly apoptotic cell death. These observations are in agreement with the *in vivo* and *in vitro* findings pointing to apoptotic [13,14,23,28] and antiangiogenic effects of the alkylglycerols found in Ecomer [15,29]. Despite structural similarities between synthetic and natural alkylglycerols and similarities in antitumor effects [30,31], as well as their effects on angiogenesis and apoptosis [15], it should be mentioned that shark liver oil contains, in addition to alkylglycerols, also methoxy-derivates of alkylglycerols and squalen. It is difficult to speculate which component of Ecomer is responsible for its apoptic effect; squalen, for example, has been indicated as a possible anticancer agent [15]. There is also quite a large body of evidence indicating the potentially antitu-

mor effects of methoxyderivates. Recently Wang et al. demonstrated the differentiation-promoting effect of methoxyalkylglycerol (2 methoxyhexadecyl glycerol MHG) in human colon cancer cells [32].

Already in the early 1970s Ando et al. [33] revealed that methoxyhexadecyl glycerol had a clear inhibitory effect on melanoma B16, Lewis lung tumor, MCA sarcoma MCG101, and lymphomas LEX and P1534. More recently it has been demonstrated that naturally occurring methoxy-derivates of alkylglycerols inhibit cellular proliferation and restrain independent growth and cellular growth in the human prostate cancer Uncap and DU-145 [32]. These observations may indicate that methoxy-derivates rather promote differentiation of different cancer cells, not directly influencing cancer cell death. It would be possible to speculate, on other hand, about a possible synergistic action of alkylglycerols with their methoxyderivates and squalen with respect to general antitumor activity, the alkylglycerols being presumably responsible for the observed apoptosis and/or necrosis of cancer cells. Assuming a similarity between the action of naturally-occurring and synthetic ether lipids, and taking into account the early observations that both are incorporated mainly in the cancer cell membrane, it seems likely that the cytotoxicity of Ecomer may result from oxidative stress involving iron-induced lipid peroxidation, as proposed by Wagner et al. [34]. The generation of lipid oxyradicals under the effect of ether lipids is a rapid process that takes place in a few minutes, in contrast to cytotoxicity, which – as observed in our experiment – is a delayed, long-term process. This long time lag could be the result of a series of intermediate steps, such as propagation of peroxidation or overcoming antioxidative defense systems, such as cystein-dependent, intracellular, anti-oxidative pathways stimulated by Bcl-2. On the other hand, Verdonck [28] reported that ether lipids could kill acute leukemic blasts by inducing apoptosis, which occurred within 15 min. Likewise, Mollinedo reported apoptotic death for leukemic cells induced by ether lipids after only 6 min. of incubation [23]. Interestingly, the same group (Mollinedo F et al.) showed that the varying content of unsaturated lipids in cell membrane may determine the degree of generation of lipid peroxides. The membrane-dependent effects of ether lipids, and particularly the alkylglycerols, caused disturbances in membrane fluidity and permeabilization of neoplastic cell membranes [23]. These membrane effects were also shown to be responsible for the alkylglycerol-dependent activation of macrophages and subsequent phagocytosis [35].

Further evidence has come from the observation reported by Wagner, that prior enrichment of cells with polyunsaturated fatty acids promoted apoptosis and enhanced generation of free radicals, while cancer cells with a low content of polyunsaturated fatty acids in their membranes were oxidatively silent and resistant to the effect of ether lipids [34]. The same group explained the sensitivity of HL-60 cells and the resistance of the other leukemia cell line, K-562, by the observation that K-562 was found to be oxidatively silent. Thus the difference in oxidative susceptibility may explain the observed differences in the percentage of cell death observed in our experiment in the different human cancer cell lines. One of the mechanisms inducing the higher generation of free radicals described in connection with ether lipids is their influence on two protooncagenes, c-fas and c-jun, encoding two components of transcription factor AP-1 [36]. AP-1 is known to induce increased production of proinflammatory cytokines and production of free radicals. The increased activation of AP-1 can possibly explain both the induction of apoptosis, by increasing the free radical-dependent oxidative stress, and also the enhancement of the tumoricidal activity of macrophages associated with alkylglycerols [36].

A possible mechanism explaining the differences we found in the effects of alkylglycerols on different cell lines may depend on the differences in the affinity of alkylglycerols to the cell membrane of different neoplastic cells, as evidenced by varying content of alkylglycerols in 17 different human tumors [3]. The same group explained the significantly higher content of alkylglycerols in neoplastic cells in comparision with normal cells by the absence of an alkyl ether-cleaving enzyme (etherase) that is found in liver and other healthy cells [37].

Although a clear concept of the molecular target for alkylglycerols and ether lipids has yet to emerge from these diverse findings, it is possible that there is no one single mode of action, but rather a series of critical events which can act in concert to induce apoptosis and to inhibit tumor cell growth. It is also possible that this complex mode of action depends on the presence of three different components in shark liver oil: alkylglycerols, metoxyderivates of glycerols and squalen.

CONCLUSIONS

The results of the present study show a clear apoptosis/necrosis-inducing effect of shark liver oil (Ecomer®) in three different cell lines of human prostate cancer, and in human mammary carcinoma cells line. This effect seems to be specific for particular cancer lines, as no such effect was observed the human ovarian carcinoma cells. Further studies are needed to elucidate possible therapeutic application of the alkylglycerols present in the shark liver oil of Ecomer.

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