Current understanding of the efficacy and safety of alkoxyglycerides and the refined fraction of Ecomer shark liver oil. Publication 2: Analyzing the Results of Clinical Trials

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Modern views on the efficacy and safety of alkylglycerols and purified shark liver oil Ecomer®.

Publication 2: analysis of the results of clinical studies

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SUMMARY

From an array of bibliographic sources of varying degrees of reliability, we identified and analyzed the results of clinical studies of alkoxyglycerides (AKG), refined shark liver oil "Ecomer" (Natumin Pharma, Sweden) and crude shark liver oil. The existence of an evidence base for the use of AKG and a standardized product from liver oil of deep-sea sharks of the northern seas "Ecomer" (Ecomer®) as an immunomodulating and antitumor agent in foreign clinics has been established. We have not found the results of the use of alkoxyglycerides and the standardized product from the liver oil of deep-sea sharks of the northern seas "Ecomer" (Ecomer®) in domestic clinics.

The efficacy, safety and range of pharmacotherapeutic activity of products based on shark liver oil depends on the qualitative composition, the quantitative content of the ingredients, as well as the degree and nature of the purification of the feedstock. Therefore, the extrapolation of the evidence base revealed by us in terms of the immunomodulatory, hypocholesterolemic, antitumor effect and absence of toxicity of AKG and the standardized product "Ecomer" cannot be considered legitimate to a cheaper line of dietary supplements for shark liver oil of various degrees of purification and quality.

Key words: alkoxyglycerides (AKG), Shark Liver Oil (MPA), Ecomer, Clinical Research.

RESUME

We have identified and analyzed the results of clinical studies of alkylglycerols (AKG), purified shark liver oil (Ecomer®, NatuminPharma, Sweden) and crude shark liver oil in bibliographic sources of varying degrees of reliability. Studies abroad (worldwide) recently confirmed the earlier performed studies by A. Brohult (for AKG) and clearly verified anticancer and immunomodulatory effect of Ecomer®. We have not identified the reliable results of applying of AKG and standardized product from the deep-sea shark liver oil of the northern seas Ecomer® in Russian clinics.

Extrapolation of the evidence base of the immunomodulating, antitumor effect and

lack of toxicity AKG and standardized product Ecomer® to cheaper shark liver oil food supplements of varying purity and quality is incorrect.

Keywords: alkoxyglycerols (AKG), shark liver oil, Ecomer®, clinical trials, clinical studies.

Bibliographic data on preclinical studies concerning the specific pharmacological activity and safety (toxicity, mutagenicity) of products from crude (unfractionated) [4, 6, 7, 11, 12, 17, 37, 59, 70, 75, 87] and refined liver fat sharks [5, 15, 51, 52, 71–73, 77], as well as fractions of alkoxyglycerides (AKG) [1, 5, 16, 38–41, 49, 65, 68, 85] and squalene [11, 53, 54, 75, 76, 87] are extremely heterogeneous. Previously, we were able to substantiate the inadmissibility of extrapolating the results of toxicological and pharmacological studies of standardized products containing refined fractions of shark liver fat (oil) to a variety of products (dietary supplements) from crude oil (various biological species of the genus shark) that have not been subjected to similar tests [3] ...

Reliable results of experimental studies allow us to consider the proven immunomodulatory and antitumor types of action of purified AKG fractions, as well as the standardized product from shark liver oil "Ecomer" [3]. These data are consistent with the traditional use of shark liver oil in Sweden and Norway [9, 45, 48]. It is also known that originally shark liver oil was mined by Scandinavian sailors for the treatment of skin and colds, cancer and diseases of the endocrine glands, which are now classified as lymphadenopathies [9, 45, 51, 76]. Ecomer® refined shark liver oil[one]) or its individual components, for example AKG, are now used in oncology (including in rehabilitation treatment) [32–34, 42, 45, 48, 50–52, 56, 58, 61, 68, 69], as well as as immunostimulants (immunomodulators) [42, 45, 48, 49, 56, 61, 67–69]. A reliably established effect of shark fat-based production on the synthesis and metabolism of a number of amino acids in the body has been reported [49] and a pronounced antioxidant effect [1, 49, 67, 69]. At the same time, the results of clinical studies of individual fractions or types of products based on shark fat are often unreasonably transferred to the feedstock or numerous dietary supplements to food of different composition and quality, for which such studies have not been conducted.

Relevant is an information and analytical study the results of clinical trials of the entire range of products based on shark liver oil of various origins, composition and quality (AKG fractions, squalene, crude and refined oils), in a comparative aspect.

The purpose of this work is to collect, summarize and analyze the results

clinical studies of the spectrum of pharmacotherapeutic action of AKG, standardized purified fraction from deep-sea shark liver oil (northern seas) "Ecomer" (Ecomer®, Natumin Pharma AB, Sweden) and crude shark liver oil (MPA). Taking into account the results of the previous analysis of experimental data [3, 45], we made an attempt to generalize information about clinical studies of the product "Ecomer", present on the domestic market, in terms of their antitumor, immunomodulatory and hypocholesterolemic action.

Materials and methods

As objects of research, we used bibliographic sources of a high level of reliability of three categories: domestic and foreign publications in scientific periodicals, abstracts of dissertations and monographs. In carrying out this study, the following methods were used: information and analytical, historical, content analysis, systematization, grouping, ranking, comparative and structural analyzes.

Results and discussion

On the first stage research we identified range species pharmacotherapeutic action of various products based on shark liver oil, with clinical confirmation. Then the results of clinical studies found in reliable bibliographic sources were systematized according to the types of pharmacotherapeutic action identified separately for each type of product: AKG and squalene fractions, crude shark liver oil (MPA) and highly refined fraction of oil from the liver of deep-sea sharks of the northern seas "Ecomer" (Ecomer®). Particular attention has been paid to safety issues and side effects assessment in clinical trials of various shark liver oil products.

According to T. Iannitti and B. Palmieri (2010), MPA is traditionally (Sweden, Norway) used as an agent that increases resistance to infections and for the treatment of cancer [28-30, 45, 48, 56], on the basis of that cancer and infectious diseases are not detected in sharks [28, 30, 45][2]... Experimentally and clinically, AKG has been proven to be effective against the side effects of radiation therapy (for radiation damage) and as a means for nonspecific stimulation of the immune response [18–26, 45, 48]. The ability of AKG to change the permeability of the blood-brain barrier, revealed in recent years, is very interesting [45], but the published data are experimental in nature. We also found works on the study of the hypocholesterolemic effect of MPA [6-8].

According to M. Krotkiewski (University of Gothenberg, Sweden - Institute of Clinical Neuroscience, Sahlgrenska Academy), who summarized in 2010 the entire array of results of preclinical and clinical study of Ecomer® in research centers in Poland, two main types can be considered proven the actions of this standardized product. The antitumor effect of Ekomer is mainly due to the presence of methoxy derivatives of AKG,

immunomodulatory - unmethylated AKG [52].

Immunomodulatory action. According to numerous data obtained in different countries in a number of reliable preclinical studies [3], the main links of the immune system are directly or indirectly activated by AKG from MPA[3] or AKG of synthetic origin[4]...

Back in the 50s and 60s. XX century animals have shown the ability of AKG to stimulate hematopoiesis, erythropoiesis, thrombocytosis, granulocytosis [31, 66]. In the 1980s. published data confirming that AKG increase the functional activity of macrophages [44, 62, 63, 83-86], which leads to an increase in Fc-receptor-mediated phagocytosis and humoral immune response [13].

In the course of further studies under laboratory conditions, it was reliably shown that AKG activate granulocytes [67]: blood sampling was performed from the peripheral vein of healthy volunteers; neutrophilic granulocytes were isolated and incubated with AKG, then their activity was determined by chemiluminescence. Such incubation of granulocytes increased their functional activity and led to an increase in the intracellular concentration of Ca^{2+} [67]. Evidence of the rationality of the practical use of AKG as immunostimulants (immunomodulators) has been published [45, 49, 67–69]. It is assumed that AKGs can control the immune response by modifying platelet activating factor (PAF) and production of diacylglycerols (DAG), while squalene from MPA increases the activity of antigen-presenting cells and induces an inflammatory response [56].

In a study with standardized MPA, 13 volunteers took it daily based on a daily dose of 3.6 g of AKG, 750 mg of polyunsaturated fatty acids and 3.6 g of squalene [55]. After four weeks of treatment, the volunteers increased the activity of neutrophilic granulocytes, increased the level of the C4 component of complement and the ability of peripheral blood monocytes to produce interleukin 2. According to the authors, the addition of MPA to the diet has a beneficial effect on the body during infections [55].

A special study by the same authors (2005) is dedicated to Ecomer®. In a group of 25 patients with frequently recurrent aphthae, who took 3 capsules of Ecomera daily for 3 months, a decrease in the number of relapses of the disease and a decrease in the volume of lesions of the oral mucosa were reliably shown. Since MPA has both systemic and local action, Ecomer capsules were chewed before swallowing. The treatment led to a significant increase in the functional activity of neutrophilic granulocytes. The researchers concluded that Ecomer® contains ingredients with immunomodulatory effects, and its regular use has helped to reduce the severity of aphthous stomatitis. The Ecomer® effect persisted for several months after completion of treatment [55].

When examining the cytokine status[5] In a single-center (Research Institute of Nutrition, Russian Academy of Medical Sciences, 2007), an open, randomized controlled study, it was shown that the level of interleukin 1b while taking MPA statistically significantly decreased in patients of the main group by 46%, in the comparison group - by 4%. The study included 40 patients with coronary artery disease with arterial hypertension (GB I-II grade) and hyperlipidemia (the same number of patients were included in the control group). The chemical composition, characteristics of authenticity and quality indicators of the investigated product are not given by the authors [6–8].

In addition to those described above, a number of other publications are devoted to the study of the immunomodulatory effect of the standardized highly purified MPA of the northern seas "Ecomer®".

The effect of "Ecomer" on various parameters of the immune system was studied in a cross-over, double-blind, placebo-controlled study in healthy volunteers [5, 15, 74]. The subjects took Ecomer (group 1) and placebo (group 2) for 15 days. After the 30-day period (to eliminate the drug), both groups received another treatment for another 15 days. Blood samples were taken before and after each treatment period. In group 1, an increase in the number of lymphocytes and an increase in the chemiluminescence of granulocytes and / or blood monocytes were found, which allowed the authors to draw a conclusion about the positive effect of Ecomer on the anti-infectious defense of the body [5, 15, 74].

According to the results of a number of studies carried out in university clinics in Poland and Sweden, their authors found it possible to state a significant increase in antibody production, chemokinetic activity of spleen cells and an increase in the relative number of B-lymphocytes under the influence of Ecomer [50–52, 61]. In their opinion, this is what determines the validity of the use of "Ecomer" in the case of a decrease in the humoral immune response [52, 61]. Thus, based on the results of numerous studies, it can be considered proven that Ecomer® increases the functional activity of granulocytes and macrophages, has a beneficial effect on both T-cell and B-cell links of immunity,

Antitumor and other types of action of products based on IPC in oncology.

The first positive results were obtained by Brohult and Holmberg (1954) in the treatment of leukemia in children: the positive effect of preparations containing AKG esters and unsaponifiable fractions of bone marrow lipids on the maturation and differentiation of blood leukocytes was established [10, 18].

In 1963, A. Brohult published a dissertation on the use of AKG fraction isolated from the liver of a Greenland shark (Somniosus microcephalus) against the background of radiation therapy by molecular distillation followed by hydrolysis. In patients with cervical cancer, it has been shown that a decrease in

the content of leukocytes and platelets in the blood (a complication of radiation therapy) is much less pronounced against the background of the administration of AKG [19], as is the frequency of radiation injuries [22, 23]. If AKG was administered before the initiation of radiation therapy, the incidence of fistula formation also decreased by 47% [25].

The gynecological departments of the Swedish Umeå University and the Royal Academy of Engineering Sciences in Stockholm studied the effect of AKG on the incidence of damage during radiation therapy for cervical carcinoma [23]. As a result of many years of clinical studies, it has been shown that the use of AKG can not only significantly reduce the degree of damage during radiation therapy, but also significantly increase the overall survival and life expectancy of irradiated patients. At the same time, it has been reliably shown that mortality at the late stages of the development of the tumor process is significantly reduced in the age groups of the group of patients under 60 years of age [26].

Special works are devoted to the analysis of tumor growth regression against the background of the use of AKG. The study used a concentrated MPA "AT 18" with a content of 85% AKG [24]. It has been shown that regression of cervical tumor growth (carcinoma) and a decrease in the frequency of radiation damage after irradiation have a direct effect on patient survival, and the incidence of complications of radiation therapy is markedly reduced when taking AKG. Combined lesions (resulting from radiation damage to tissues and residual and / or recurrent tumor growth) are detected in 1/3 of patients on the background of prophylactic use of AKG 1 week before the start of radiation therapy. At the same time, already a 7-day prophylactic course of AKG leads to a noticeable (30%) reduction in damage at the later stages of the development of the tumor process [24].

In groups of patients with less pronounced (non-combined) radiation injuries, the severity of complications decreased in half of the cases against the background of AKG [26]. A more detailed analysis of the effect of AKG on the frequency, nature and degree of radiation damage was published in special works [23, 47]. A. Brohult et al. also considers it useful to take long-term AKG after the end of the course of radiation therapy, while paying attention to the fact that the regression of tumor growth is associated with "a non-toxic natural substance that is present in the human body" [24], since AKG is normally present in the organs and tissues of a healthy human, including in breast milk of lactating women [3, 22-24, 26, 42].

Of practical interest for oncologists is the analysis of the effect of AKG (concentrated MPA "AT 18" with a content of 85% AKG) on survival and other parameters depending on the nature of injuries during radiation therapy [47]. It has been shown that the traumatic consequences of radiation injuries (with radiation therapy) in most cases are cured within 6–12 months. These lesions are painful for the patient but have little effect on survival. At the same time, in the case of patients with combined lesions (radiation damage plus the development of the tumor process and its complications), the situation is fundamentally different: almost all of them die (98–100%) within five years. The researchers found that with prophylactic use of AKG, combined lesions occur in only one third

cases compared with a control group of patients who were treated with radiation therapy alone. In addition, it has been shown that if in 11.6% of radiation therapy cases, bladder injuries (stage III) and rectal injuries (stage IV) with the formation of fistulas are recorded, then against the background of prophylactic use of AKG, the percentage of such injuries decreases to 6.2 in the group (that is, by 47%) [47].

In 1998, R. Firshine received a patent for a cancer treatment method using AKG in combination with chemotherapy [33, 34], since a whole series of works has shown that synthetic drugs are much more effective in chemotherapy if their administration is accompanied by AKG. The synergistic effect is manifested in a significantly more active destruction of tumor cells, compared with chemotherapy without concomitant administration of AKG [33, 34].

More recent studies have shown that the mechanisms of antitumor activity of various ingredients of shark liver oil (AKG, squalene) can be different and based on the induction of apoptosis of tumor cells, suppression of signaling, inhibition of angiogenesis, and improvement of transmembrane transfer of cytotoxic agents [56]. The mechanisms of action of AKG are considered to be well understood, with cytokines playing a key role in stimulating immune defense and preventing cancer [35, 46]. Another interesting scenario for the implementation of the antitumor activity of AKG consists in the accumulation of O-alkyl groups in cancer cells, which lose their ability to multiply uncontrollably [57] as a result of low O-alkyl-monooxygenase activity of the enzyme (or its absence), followed by the accumulation of lipid ethers in tissues,

Based on the results numerous studies made conclusion that MPA can be useful in the complex therapy of certain types of cancer and in the correction of conditions caused by an inadequate immune response [45, 56, 81].

A number of studies have been carried out in Polish and Swedish oncological research centers on the serial products Ecomer® [50–52, 61] in order to prove the effectiveness of this product in oncology and to reveal the mechanism of its antitumor action.

At the Institute of Oncology in Warsaw, the proliferation of prostate cancer cells under the influence of Ecomer has been studied. The number of derived colonies of three types of human prostate cancer cells (DU-145, PC-3, PCa-2b), distributed in the minimum necessary medium (MEM), was evaluated (by the method of planting efficiency). The number of colonies of all three types of cells decreased to 0 at a concentration of "Ecomer" 1 mg / ml. For DU-145 and PCa2b cells, a significant decrease in the number of colonies was observed already at a concentration of 0.1 mg / ml, for PC-3
- at a concentration of 0.05 mg / ml [51, 52]. In a similar study on DU-145 type prostate cancer cells under the influence of Ecomer, the number of colonies decreased to 0 - the result was even better compared to Taxol [51, 52, 61]. In the colonies of all three types of tumor cells "Ecomer" (in

flow cytometry) increased the number of necrotic and apoptotic cells and induced a strong cytotoxic effect, while the standard cytostatic drug did not show such effects [51, 52].

The efficacy of Ecomer in prostate cancer was confirmed in a long-term placebo-controlled, randomized, double-blind GCP-clinical study led by Professor T. Demkov, which was carried out after hormonal therapy for 5 years. The control group received placebo, the second group received Ecomer before, during and after radiation therapy, the third - only before radiation therapy. The study took into account: quality of life, blood picture (erythrocytes, leukocytes), direction of the immune response, inhibition of tumor growth and metastases, mortality [51, 52]. Studies carried out in Poland fully confirmed the results obtained by A. Brohult on AKG fractions [18–26],

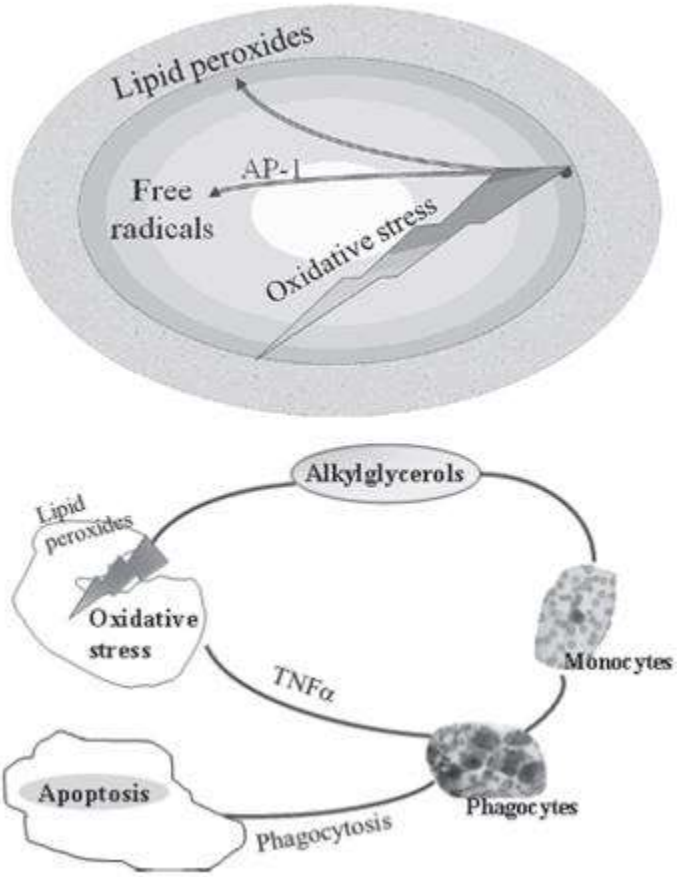
In particular, it has been shown that Ecomer prevents the development of leukopenia against the background of suppression of bone marrow function during or after radiation therapy [51, 52], as well as thrombocytopenia during irradiation or administration of cytostatics [51, 52] (statistically significant prevention of leukopenia was revealed and thrombocytopenia). A significant decrease in the frequency of radiation damage (side effects and complications) as a result of radiation was also shown, as well as a direct cytotoxic effect of Ecomer on tumor cells. The ability to more quickly restore bone marrow function under the action of Ecomer, inhibition of tumor growth and the process of metastasis has been established [51, 52]. At the same time, the survival rate of patients (in particular, those with cervical cancer) significantly increased if Ecomer was started before the course of radiation therapy [51, 52, 61], which is also consistent with the data obtained earlier for AKG. When studying the mechanisms of antitumor action, it was found that the degree of incorporation of esterified lipids (AKG, Ecomer) into the cell membranes of tumor cells is two orders of magnitude higher (almost 100 times) than in the case of normal cells. This difference is explained by a decrease in activity (or complete absence) in cancer cells of enzymes that destroy AKG [51, 52, 61].

Ecomer, like other esterified lipids (AKG), blocks intracellular signaling: inhibition of inositol-3-phosphate (IP3) formation is followed by inhibition of intracellular Ca release^{++}, inhibition of protein kinase C, and, as a consequence, the proliferation of cancer cells is inhibited [51, 52, 61]. The increased formation of free radicals, in particular, lipid peroxides, goes through the stimulation of the transcription factor AP-1, followed by an increase in the number of free radicals, an increase in the concentration of lipid peroxides in cell membranes, impaired permeability of cell membranes and increased penetration of cytostatics when administered together with Ecomer. The destruction of the membranes of cancer cells leads to the release of AKG into the extracellular space, followed by activation

macrophages, release of tumor necrosis factor α (TNFα) and increased phagocytosis. All these mechanisms contribute to increased necrosis and apoptosis of cancer cells during therapy [51, 52, 61] (Fig. 1).

The established antiangiogenic (preventing the formation of new blood vessels as a condition for tumor growth and metastasis) effect of Ecomer allows us to classify it as an effective and promising antiangiogenic agent [51, 52, 61, 77]. According to modern concepts, the proposed mechanism of antiangiogenic action is as follows: migration of cancer cells to the angiogenic factor (basal fibroblast growth factor - bFGF) is inhibited, apoptosis increases[6], the binding of angiogenic growth factors to their membrane receptors is inhibited [77, 79]. Confirmation of the pronounced effect of inhibition of the growth of the vascular network by "Ecomer" by the putative antiangiogenic mechanism was obtained in an experiment on lung cancer cells obtained from 13 patients [78]. Interestingly, the oral administration of squalene, in contrast to Ecomer, did not affect the tumor mass. At the same time, angiogenesis was significantly reduced when Ecomer was taken orally in combination with squalene [79].

In another study, an anti-angiogenic test was performed after a 14-day intake of Ecomer. In addition to taking into account the number of newly formed blood vessels, M. Krotkiewski et al. (1999) measured the proliferative activity of tumor cells. Both revealed effects were significant and correlated with each other [50, 52].



Rice. one . Ecomer's mechanism of actionKrotkiewski M (2010)

Very interesting results were obtained when studying the synergistic effects of Ecomer with probiotics [52]. For the first time the effect on the positive interaction of lactobacilli with AKG was noted by A. Brohult back in 1960 [45]. The design of the current study is based on the data on the pronounced effect of lactobacilli on the stimulation of the humoral and cellular immune response [60], as well as on the antibacterial activity of Ecomer against Corynebacterium hofmani Streptococcus pneumoniae, Staphyloccocus pyogens, Streptococcus pyogens, Streptococcus virginia. This antibacterial activity indirectly supports the growth of lactic acid bacteria, contributing to the normalization of the intestinal biocenosis. Lactic acid bacteria of probiotics enter the large intestine in a viable intact form and form active colonies, preventing the adhesion of virulent pathological bacterial species, and co-administration with AKG increases their proliferative potential. A synergistic effect arises due to various ways of modulating antibody production [27, 52]. Information about the antibacterial action of "Ecomer" is consistent with the data of R. Nowicki et al. (2007) on the antibacterial and antifungicidal effect of MPA, which allowed the authors to recommend it to patients suffering from atopic dermatitis [64]. Thus, refined shark liver oil "Ecomer" (Ecomer®), as well as its individual components (AKG), are now widely used abroad in complex and restorative treatment in oncology [5, 50–52, 61]. A synergistic effect arises due to various ways of modulating antibody production [27, 52]. Information about the antibacterial action of "Ecomer" is consistent with the data of R. Nowicki et al. (2007) on the antibacterial and antifungicidal effect of MPA, which allowed the authors to recommend it to patients suffering from atopic dermatitis [64]. Thus, refined shark liver oil "Ecomer" (Ecomer®), as well as its individual components (AKG), are now widely used abroad in complex and restorative treatment in oncology [5, 50–52, 61]. A synergistic effect arises due to various ways of modulating antibody production [27, 52]. Information about the antibacterial action of "Ecomer" is consistent with the data of R. Nowicki et al. (2007) on the antibacterial and antifungicidal effect of MPA, which allowed the authors to recommend it to patients suffering from atopic dermatitis [64]. Thus, refined shark liver oil "Ecomer" (Ecomer®), as well as its individual components (AKG), are now widely used abroad in complex and restorative treatment in oncology [5, 50–52, 61].

Hypocholesterolemic action MPA It was established v single-center (Research Institute of Nutrition, Russian Academy of Medical Sciences, 2007), an open, randomized controlled study on 40 patients with coronary artery disease with arterial hypertension (HD I-II degree) and hyperlipoproteinemia on the background of a hyponatric antiatherogenic diet. After 3-week therapy in all patients, the level of systolic and diastolic pressure, total cholesterol and low density lipoproteins significantly decreased, and the concentration of triglycerides tended to decrease. The authors do not report on the chemical composition, qualitative and quantitative characteristics of the shark liver oil included in the study [6, 8]. Earlier, the same authors showed an improvement in anthropometric parameters, lipid profile, immunological status and general condition of rats with coronary heart disease and arterial hypertension on the background of a diet enriched with MPA [7].

Among other types of action, the positive effect of taking AKG in lymphadenopathy [51, 76] and atopic dermatitis [64] is considered reliably proven.

Safety. MPA has been eaten for several centuries [3, 5, 9, 15, 19-21, 51, 61, 76], and currently its annual consumption exceeds 250 tons [5]. Nevertheless, there is evidence that unpurified MPA, due to its constituent squalene (a cholesterol precursor [80]), increases the plasma cholesterol level in humans and animals [3, 61, 75, 87].

In 2002, Z. Zhang et al., Studying the toxicological effect of MPA, crude from squalene, on hamsters, reliably showed that the level of cholesterol increased by an average of 19% compared with refined oil [61, 87]. According to experts, such a side effect is unlikely when taking Ecomer®, since this dietary supplement, taking into account the results of experimental studies, is purposefully purified from squalene (with a residual amount of no more than 1%) during the production process [5].

There are also other precautions for taking MPA products that are not squalene-free. In particular, cases of lipoid pneumonia (in Southeast Asia) caused by MPA, which was inhaled through the nose for the treatment of upper respiratory tract infections, have been described [3, 11, 53, 54]. The causative agent of the disease is presumably squalene, so the risk of lipoid pneumonia with Ecomer® is excluded [5].

Clinical studies of Ecomer® in oncological diseases did not reveal any side effects of this dietary supplement to food [5, 51, 52, 61]. The results of an information and analytical study on the preclinical study of the safety of MPA and Ecomer were published by us earlier [3].

Bioavailability. We found no data on the study of the AKG fraction from Ecomer®. AKGs are well absorbed [5, 14] and therefore cannot cause bioavailability problems that could affect the safety or efficacy of the formulation used in Ecomer® [5].

Thus, in the opinion of leading world experts and based on

results of preclinical and clinical studies, Ecomer® is clinically safe; there are no contraindications to its long-term use (in officially recommended dosages as a dietary supplement to food) [5, 51, 52, 61].

Conclusion. According to the results of foreign studies, natural product (dietary supplement for food) of animal origin "Ecomer" is recommended to increase resistance against various infections, during the period of convalescence after prolonged and severe diseases, in the complex correction of immunodeficiency states, disorders of intestinal biocenosis, in oncology - together with chemotherapy and / or radiation therapy. Its direct cytotoxic effect on tumor cells, as well as inhibiting tumor growth and slowing metastasis, preventing the occurrence of leukopenia and thrombocytopenia, reducing the side effects of radiation therapy, normalizing bone marrow function (without its overstimulation), has been proven. In the Russian Federation, Ecomer® is approved for sale as a duly registered dietary supplement for food - a source of alkylglycerols (alkoxyglycerides, AKG).

conclusions

1. As a result of the conducted information and analytical research revealed an extensive evidence base for a wide range of pharmaco-therapeutic activity of dietary supplements for food "Ecomer" ("Natumin Pharma AB", Sweden).

2. The published results of clinical trials confirm the types of action of the standardized product "Ecomer®" identified in animals: immunomodulatory, antitumor, radioprotective (reducing the traumatic effects of radiation therapy).

3. Efficiency, safety and spectrum of pharmacotherapeutic the activity of products based on shark liver oil depends on the qualitative composition, the quantitative content of the ingredients, as well as the degree and nature of the purification of the feedstock.

4. Extrapolation of the evidence base identified by us in part The immunomodulatory and antitumor effect of purified fractions of alkyl glycerides and the standardized product Ecomer® on a much cheaper line of dietary supplements for shark liver oil of various degrees of purification and quality cannot be considered legitimate.

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[one] Later, a list of tumors (solid tumor) found in sharks was published [32, 45]

[2] AKG was first discovered in shark liver oil in 1922 [82]. In natural sources, they are always found as esterified fatty acids [45].

[3] AKGs were first synthesized in 1930 [58].

[4] The study was conducted taking into account the decisive role of cytokines in immune responses.

[5] A pro-inflammatory cytokine that plays an important role in the development of cardiovascular pathology, and in particular, atherosclerosis.

[6] The results are completely consistent with the data previously obtained in animals: AKG stimulate hematopoiesis, erythropoiesis, thrombocytosis, and granulocytosis [31].

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