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MEDITERRANEAN AND BLACK SEA ORGANISMS AND ALGAE FROM MARICULTURE AS SOURCES OF ANTITUMOR DRUGS

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Mussels and tunicates cultivated in Mediterranean and Black Sea are the sources of antitumor drugs. Three compounds isolated from these animals (ET-743, aplidin and bryostatin-1) are on the II–III stages of clinical trials. Carotenoid fucoxantin that is present in edible brown algae possesses antitumor activity. The consumption of brown macrophyts decreases the risk of cancer development.
***Key Words*: cultivated mussels, tunicates, ET-743, aplidin, bryostatin-1, fucoxantin, edible brown algae.**

Mussels and oysters are the molluscs, the large mariculture of which is being developed in Ukraine. Their meat is the delicacy and a dietary medication. Few drugs possessing cytotoxic and antitumor action have been isolated from the soft tissues of mussels [1]. The active ingredients are related to different classes of chemical compounds: carbohydrates, carbohydrate–protein complexes and lipids. Some lipid fractions possess a marked antitumor effect *in vivo*. From gonades of the mussel *Mytilus galloprovincialis* cultivated near Crimean shores, we have isolated the lipid fraction (up to 0.5–0.7% of crude weight). The antitumor activity of fraction against experimental murine tumors was assayed. It inhibited by 58–76% the growth of three experimental tumors (Lewis lung carcinoma, transplantable mammary adenocarcinoma 755, AKATOL adenocarcinoma of the large intestine) with subcutaneous injections in the doses of 5–80 mg/kg during 5 days [2]. Using the methods of electronic paramagnetic resonance, electrochemistry in non–water medium, and liquid chromatography, it was determined that the fraction is enriched with vitamin E and its derivatives. That drug has revealed no toxicity *in vivo* in the studied range of concentrations, and we suppose that its antitumor effect may be mediated by immunomodulative activity [2]. Antitumor drugs isolated from mussels are not individual chemical compounds. However, in oncological practice mainly individual chemical substances are used. In the future, such compounds should be isolated from sea mussels. At present one may only recommend to enrich the diet of the patients with marine products, especially ones on the base of fresh mussels to obtain the maximal amount of biologically active compounds.

In the process of using mussel–oyster farms, the collection of other hydrobionts that appear and vanish during seasonal succession in overgrowth communities is also possible. The next potential candidates for being a source of antitumor preparations are tunicates. A large biomass of tunicate *Botryllus schlosseri* (2–2.5 kg/m^2) is grown by mussel collectors in the Crimea. Alcaloid ecteinascidin (ET–743) has been isolated from the Mediterranean tunicate *Ecteinascidia turbinate*. It has already undergone Stages (Phase) III of clinical trials in Europe and USA [3]. ET–743 (commercial mark Yondelis) is considered to be an active drug for the therapy of sarcomas and few other tumor types and may be used in combination with the known cytostatics of platinum group. In the last case, the synergism of natural and synthetic drugs is registered, whilst no adaptation to classic chemopreparations is observed [4]. It is shown that ET–743 may be used in pediatrian oncology as well, and has been already applied on the therapy of more than 2000 patients [3].

The interesting compound aplidin (Apl) was isolated from the other Mediterranean tunicate *Aplidium albicans* [5] and presently is on the stage II of clinical trials in Europe; Apl has been already tested in 200 patients [6] and is supposed to be effective in the therapy of solid tumors and leucosis [5]. That compound is an oxidized form of didemnin B, the first individual drug isolated from the marine source and applied for clinical studies; however, due to its high toxicity, the preparation was withdrawn from Stage II of clinical trial. Didemnin B was isolated from tunicates of the family *Didemnidae*. The content of ET–743 and Apl in the natural sources is very low (10^{-5}%). That's why it is reasonable to cultivate them [7]. The cultivation of the listed species of tunicates may be carried out in different regions (Mediterranean, near the shores of Florida) and may be performed as well in Crimea for the creation of the native source for production of antitumor preparations.

The above mentioned Mediterranean and Black Sea tunicates are poisonous during the period of intense development and growth. Other inhabitants will not grow close to them even where favorable conditions are created in collectors. Mariculture of tunicates doesn't cause special difficulties [7].

The mariculture source of antitumor preparations is already developed [7]. The macrocyclic lactone (bryostatin–1) considered to be the most studied of the new antitumor drugs in USA was isolated from bryozoan

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Bugula neritina [8]. Stage II of the clinical trials demonstrated that bryostatin–1 may be used in combined chemotherapy with taxol and cysplatine for the treatment of different types of cancer — breast and lung cancer, melanoma etc. [5]. Its mechanism of action as well as that of ET–743 and Apl, has been studied. The pharmacokinetics is also described.

All mentioned species of marine organisms have the analogs in the Black Sea and may be used in the mariculture in Ukraine.

The brown algae growing in large communities in Black Sea are of special interest as a source of antitumor drugs [1]. Recently, carotenoid fucoxantine (Fx) possessing antitumor properties has been isolated from four edible macrophytes cultivated in the deep–water shelf in Japan [9]. It has been shown that 3 μM of Fx and 2 μM of fucoxantynol, the main Fx metabolite generated in the liver of animals, kill 50% of human prostate cancer cells [10]. This data shed the light on the results of the success of the study carried out in 50th in USSR when oncological patients received powdered brown algae *Laminaria* [11]. Then 500 patients regularly received *Laminaria* (10–15 mg of Fx daily) for 2–12 months and longer. As a result of such treatment combined with symptomatic directions, there was a gradual improvement of the general state and blood indices of a large part of oncological patients. The course of the disease became stabilized and the survival increased. In Japan, where edible brown algae are regularly consumed, the rate of incidence of breast cancer is 3–fold lower than that in USA [12].

In Ukraine, the stocks of edible Black Sea algae *Cystoseira spp.* are large enough [1], while the content of Fx may yield up to 0.36 mg/g [13].

In conclusion, cultivated marine organisms and algae may serve as a source of antitumor drugs. Their consumption is recommended, especially in regions with an unfavorable ecology.

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СРЕДИЗЕМНОМОРСКИЕ И ЧЕРНОМОРСКИЕ ОРГАНИЗМЫ И ВОДОРОСЛИ — ОБЪЕКТЫ МАРИКУЛЬТУРЫ — ИСТОЧНИКИ ПРОТИВООПУХОЛЕВЫХ ПРЕПАРАТОВ

Культивируемые в Средиземном и Черном морях мидии и оболочники являются источниками противоопухолевых препаратов. Три соединения, полученные из объектов марикультуры — ET-743, аплидин и бриостатин-1, находятся на II–III стадиях клинических исследований. В съедобных бурых водорослях содержится каротиноид фукоксантин, обладающий противоопухолевым действием. Употребление бурых макрофитов снижает риск развития онкологических заболеваний.

***Ключевые слова*: культивируемые мидии, оболочники, ET-743, аплидин, бриостатин-1, фукоксантин, съедобные бурые водоросли.**