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Anti-tumour drugs of marine origin currently at various stages of clinical trials (review)

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Oncological diseases for a long time have remained one of the most significant health problems of modern society, which causes great losses in its labour and vital potential. Contemporary oncology still faces unsolved issues as insufficient efficacy of treatment of progressing and metastatic cancer, chemoresistance, and side-effects of the traditional therapy which lead to disabilities among or death of a high number of patients. Development of new anti-tumour preparations with a broad range of pharmaceutical properties and low toxicity is becoming increasingly relevant every year. The objective of the study was to provide a review of the recent data about anti-tumour preparations of marine origin currently being at various phases of clinical trials in order to present the biological value of marine organisms – producers of cytotoxic compounds, and the perspectives of their use in modern biomedical technologies. Unlike the synthetic oncological preparations, natural compounds are safer, have broader range of cytotoxic activity, can inhibit the processes of tumour development and metastasis, and at the same time have effects on several etiopathogenic links of carcinogenesis. Currently, practical oncology uses 12 anti-tumour preparations of marine origin (Fludarabine, Cytarabine, Midostaurin, Nelarabine, Eribulin mesylate, Brentuximab vedotin, Trabectedin, Plitidepsin, Enfortumab vedotin, Polatuzumab vedotin, Belantamab mafodotin, Lurbinectedin), 27 substances are at different stages of clinical trials. Contemporary approaches to the treatment of oncological diseases are based on targeted methods such as immune and genetic therapies, antibody-drug conjugates, nanoparticles of biopolymers, and metals. All those methods employ bioactive compounds of marine origin. Numerous literature data from recent years indicate heightened attention to the marine pharmacology and the high potential of marine organisms for the biomedical and pharmaceutical industries.

Keywords: cancer; marine organisms; preparations; cytotoxic preparations; clinical studies.

Introduction

Malignant tumors create a significant social problem and have for many years continued to be the main constituent of non-infectious diseases, causing significant losses of labour and vital potential of society. In 2018 alone, around the world, there 18.1 M new cases of cancer were recorded, 9.6 M cases of death to cancer diseases, 20% of the population were in the risk group of oncological diseases and 10% of the patients were highly likely to die (Ferlay et al., 2019). According to the predictions of the experts of the World Health Organization (WHO) and the International Agency for Research on Cancer (IARC), in the period of 2012 to 2030, the global number of cases of cancer found for the first time will increase from 14 M to almost 22 M people, and will grow to 27.5 by 2040 (American Cancer Society (ACS) Global Cancer Facts & Figures. American Cancer Society; Atlanta, GA, USA: 2018). In some countries of Africa, Asia, Latin America, where many governments do not have enough resources for combating oncological diseases, the growth of morbidity is likely to reach 70% (Fidler et al., 2018). According to the data of the global statistics, by 2030, in the countries with developed and developing economies, the growth of cancer morbidity will exceed 93% a year, which is probably related to negative technogenic and anthropogenic factors, and also high level of detection of cancer diseases. In Russia, over 35% of the patients diagnosed with MT for the first time are of employable age (15–59 years). Now, the number of living people diagnosed with cancer (who have been cured or are currently struggling with the disease)

in the RF is approaching 3.5 M people (around 2.3% of the country's population). If the current situation does not change, every 4th Russian is at the risk of getting cancer, and every 9th may die of it (Petrova et al., 2015; Tjuljandin & Zhukov, 2018). Tumour diseases hold the leading positions in the mortality level, and at the same time, a colossal amount of resources is spent by the countries around the world annually to treat cancer, diagnose and prevent it at early stages (Savinkova et al., 2018).

Cancer is a whole complex of disorders in the organism, first of all, the neuro-immune-endocrine system. Tumour tissue consists of many associated cells, immunocytes, mediators, hormones, enzymes, molecules of adhesion, mesenchymal and vascular tissues. Furthermore, tumour tissue has a micro-environment and exudes signal molecules that participate in the further process of metastasis. Therefore, the methods of affecting it should be vector-like, targeted as possible, but such that would not damage healthy cells and the tissues.

Efficiency and safety of the therapy of progressive and metastatic cancer diseases, overcoming drug-resistance, combating side-effects of the anti-tumour treatment is a complex and relevant problem in contemporary medicine. Development and study of action of novel anti-tumour compounds with a broad pharmaceutical range and lowest toxicity is important for their further application as monoprparations or combined with traditional chemotherapy. Unlike the synthetic anti-cancer preparations, natural compounds are safer, have a broad range of cytotoxic activity, can inhibit the process of tumour development and metastasis by interacting with several cellular signal pathways and oncogenic factors, making it possible to

affect several etiopathogenic links of carcinogenesis at the same time and effectively treat various types of tumours (Calcabrini et al., 2017). In this connection, natural marine bioactive compounds are attracting increasing attention.

For a long time, the main approach of the pharmaceutical industry to development of such drugs was based on total screening of biologically active substances obtained from the organisms of various systematic groups of animals. The difficulty of the development of drugs from hydrobiota lies in the problems of provision of a stable raw material basis; the rare occurrence of biological species may complicate obtaining the needed amount of raw material for the development of one or another medical preparation. Despite these difficulties, over the past decade, interest in the natural products of marine origin has greatly increased. Currently, around 60% of drugs currently used in hematology and oncology are obtained from natural sources. From various marine micro- and macroorganisms, 36,000 new natural compounds have been isolated that are used in therapy of malignant tumours and may be used as promising therapeutic preparations for treatment of various diseases (Dyshlovoy & Honecker 2015; Barreca et al., 2020). As of the late 2019, in the data base of the National Institutes of Health of the USA, over 5,000 clinical trials have been recorded, and the base PubMed/Medline had over 94,000 scientific articles related to the topics of cancer diseases and preparations of natural origin, including marine, developed or used in practical oncology. High social dependence, distribution of oncopathologies, development of new technologies and approaches to treatment of cancer diseases, demand for multi-target low-toxic anti-tumour preparations have made the development and production of natural bioactive compounds among the priority directions in science and the pharmaceutical industry. Therefore, we aimed at making a review of the current data on anti-tumour preparations of marine origin at various stages of clinical trial, demonstrating the biological significance of marine organisms producing cytotoxic compounds and prospects of using them in contemporary biomedical technologies.

The work used the literature data on anti-tumour preparations of marine origin that were approved for the use and/or are underway at phases I–III of clinical trials. The paper also presents bioactive compounds of marine origin, the trials of which demonstrated their cytotoxic activity at phases I–II and are promising for further development of drugs against various types of cancer and other diseases. The review includes the data on biologically active substances isolated from Ascidiacea, sponges, mollusks, Alcyoniina, Bryozoa, marine fungi, cyanobacteria, algae. We analyzed 640 sources of the literature published between 2000 and 2021, and used 268 of them for writing the review.

Marine organisms producing cytotoxic compounds

Ascidiacea. There are known single and colonial forms that live in coastal and deepwater zones. Ascidiaceans produce a large amount of toxic secondary metabolites that protect them against predators and biofouling organisms. In the period from 1994 to 2014, from ascidiaceans, there were isolated 580 compounds with antibacterial, anti-inflammatory, anti-virulent, anti-diabetes, anti-proliferative, anti-parasitic activities (Palanisamy et al., 2017). Currently, the most efficient producers of biologically active compounds are considered the representatives of the Didemnidae, Polyclinidae and Polycitoridae families, and out of 69 representatives of *Didemnum* genus, there were isolated 212 biologically active compounds (Diaa et al., 2020). The high pharmacological potential of nonribosomal peptides, proline-rich cyclic peptides and many compounds of various chemical classes produced by ascidiaceans, and clinical application of them for the treatment of broad range of diseases, including in oncology, are well known (Diaa et al., 2020). In experiments, toxic metabolites of ascidiaceans exerted effects on DNA transcription, protein translation, processes of neurohumoral regulation, cytoskeleton (Agrawal et al., 2016; Fang et al., 2016; Negi et al., 2017; Arumugam, 2018). Practical medicine uses 4 drugs derived from ascidiaceans to treat patients suffering oncological diseases: Trabectedin, Aplidin[®], Midostaurin, Lurbinectedin.

Sponges are aquatic, chiefly marine multicellular animals that live attached to surfaces, without any true organs. Sponges have no intrinsic immune system or structures of mechanical protection such as shell or the spinal cord. Therefore, their only way to protect themselves is to produce

active metabolites that act as a means of protection against and adaptation to the environment, they have effective systems of biotransformation and detoxication that counteract the influence of DNA-damaging carcinogens (Aiub et al., 2006.). There are known 53,000 active compounds isolated from sponges and their associating organisms (Bibi et al., 2017). In the period 2001–2010, up to 30% of identified biologically active substances were isolated from them: avarols, arenastatins, halichondrin, milnamid, spongistatin, dactyloides, dictioctatin, discodermolide, hemiasterlin, laulimalide, peloruside A and zampanolide (Mehub et al., 2014; Gnanambal & Lakshmiopathy, 2016; Santos et al., 2020). Currently, 774 new compounds isolated from marine sponges and associating microorganisms have been studied and described, and 42% of them demonstrated high biological activity (Cheng et al., 2020). Preparations developed based on those compounds are efficient in treatment of metastatic cancer of the mammary gland, lymphomas. Bioactive compounds also exerted *in vitro* anti-tumour activity against other types of cancer cells (Ercolano, 2019) resulting from numerous cellular and molecular mechanisms that include protection of DNA, modulation of the cellular cycle, processes of apoptosis and anti-inflammatory activity (Calcabrini et al., 2017). Pro-apoptotic mechanisms of many compounds are not completely clear, but, nonetheless, they are known to induce several apoptotic pathways at the same time. Practical oncology uses 4 anti-tumour preparations made of marine sponges: Fludarabine, Cytarabine, Nelarabine, Eribulin mesylate.

Mollusks are broadly distributed in marine, freshwater bodies and soil. Chemical examinations of marine mollusks revealed a broad spectrum of bioactive substances produced by these organisms in order to adapt to and survive in various environments – peptides, sterines, polyketides, carotenoids, terpenes, polypropionates, macrolides, polyunsaturated fatty acids, alkaloids, nitrogen compounds, etc. According to the data of 2014, 1,145 biologically active compounds were isolated from marine mollusks, and in the period between 2014 and 2018, another 145 substances were added to this list (Summer et al., 2020). Because of the variety of chemical structures and broad range of biological activity, these substances have high cytotoxic potential (Ciavatta et al., 2017; Ahmad et al., 2018; Esmaelian et al., 2018; Avila & Angulo-Preckler, 2020). Many anti-tumour compounds reached late pre-clinical and clinical developments (Newman & Cragg, 2014). The high efficacy of anti-tumour bioactive compounds isolated from mollusks is due to their high selectivity, ability to overcome chemoresistance, alter biological characteristics of cancer cells, mechanisms of activation of caspases that take part in internal and external cellular apoptotic pathways, inhibition of angiogenesis, imbalance of tubulin and microtubules (Chakraborty et al., 2020). Oncological practice uses 4 preparations of mollusks: Belantamab mafodotin, Polatumumab vedotin, Enfortumab vedotin, Brentuximab vedotin.

Bryozoa are aquatic colonial animals, a poorly studied group (around 6,000 species are known). Many species are broadly distributed in the tropics and subtropics, the colonies have a large biomass. The amount of known biologically active substances from Bryozoa is comparatively low. This is due to the fact that the biologically active compounds have until now been being extracted by the traditional techniques, using organic solvents, with great complexity of process. The studies at different stages of clinical and pre-clinical trials demonstrated the effectiveness of active metabolites of Bryozoa, which have cytotoxic, antiparasitic, antiviral, cognitive-restoring, antidepressive, anti-spasm activities. (Ciavatta et al., 2020). About 260 medical preparations were obtained from 23 species of Bryozoa (Carroll et al., 2020). Currently, the problems of extraction and synthesis of biologically active cytotoxic compounds from Bryozoa are being broadly discussed, which gives us hope for more thorough study and use of their beneficial metabolites in practical medicine (Gomes et al., 2016).

Coral reefs are recognized as the most dynamic and variable biosystem on the planet, which contains many studied and unstudied organisms (Moeller et al., 2019). Corals are hosts of species-specific microbial communities, including bacteria and fungi that produce bioactive substances, mainly of cytotoxic activity. From coral-associated organisms, 300 biologically active substances with cytotoxic, antiparasitic, antibacterial, anti-inflammatory activities have been isolated (Hou et al., 2019). These compounds are studied as potential anti-tumour and antiviral preparations, including against SARS-CoV-2 and HIV (El-Hossary et al., 2020; Zahran et al., 2020). Many bioactive products (terpenoids, sesquiterpenes, diterpe-

nes, steroids and many other) are produced by soft corals and are promising objects for the development of various pharmaceutical preparations (Sang et al., 2019).

Marine fungi are a group of heterotrophic organisms that have traits of plants and animals. Over 1,100 species of microscopic fungi isolated are known from the marine environment, whose ancestors may have evolved in freshwater water bodies and terrestrial living places (Jones et al., 2015). The same species of fungi isolated from terrestrial and marine ecosystems synthesize various biologically active compounds (Pivkin et al., 2006.; Deshmukh et al., 2018). Some substances isolated from fungi of marine origin can exert notable anti-tumour activity through various mechanisms such as apoptosis and induction of the suspension of cellular cycle (Evidente et al., 2014). The major fungal producers of the natural products are recognized to be marine fungi of genera *Aspergillus* – 28%, and *Penicillium* – 11%. (Liu et al., 2020; Fadia et al., 2021; Youssef et al., 2021). Secondary metabolites of marine fungi include peptides, alkaloids, terpenoids, steroids, lactones, polyketides (Alves et al., 2019; Ogaki et al., 2020; El-Kashef et al., 2021). A total of 53% of the examined substances mostly displayed cytotoxic, antimicrobial and antiviral activities, and to a lower degree demonstrated anti-diabetes and hypolipidemic actions. Active metabolites exhibited high bioavailability during peroral introduction, and at the same time are less toxic for humans compared with their synthesized analogues (Youssef et al., 2019). The advantage of fungi is that they may be cultivated with high rate of reproduction.

Cyanobacteria or blue-green algae are the oldest complexly organized prokaryotic microorganisms that live in water. Cyanobacteria are a rich source of known and new biologically active compounds with strong medical potential (Shah et al., 2017). These organisms are able to produce efficient toxins and other secondary metabolites, including polypeptides, polyketides, alkaloids, lipids, polysaccharides, swinholides, terpenes with notable bioactive properties. Thus, dolastatin 10, obtained from some species of cyanobacteria and the marine mollusk *Dolabella auricularia*, gave a start to the production of its synthetic analogues – MMAE and MMAF, used in modern antibody–drug conjugates. They are aimed at cancer cells, causing their apoptotic death or affecting the processes of signal cellular transmission. Numerous studies demonstrated antibacterial, antifungal, anti-tuberculosis, immune-depressing and anti-inflammatory properties of these bioactive compounds (Vijayakumar & Menakha, 2015; Rojas et al., 2020; Demay et al., 2021). Several species of cyanobacteria, cultivated on commercial platforms to obtain bioactive substances, are used in contemporary nanotechnological systems of selective transport of drugs to the tumours (Qamar et al., 2021).

Microalgae are a group of phototrophic organisms, which includes a large number of species of single-cell algae with broad range of distribution (marine and freshwater bodies, soils). Marine algae are recognized as a rich source of various biologically active substances (Cheung et al., 2015; Martínez Andrade et al., 2018). Biopolymers of marine algae are known for their broad range of pharmacological effects: cytostatic, anti-proliferative, antimetastatic, proapoptotic, antiangiogenic, and immunomodulating, having at the same time low toxicity. Bioactive substances of microalgae can inhibit all phases of carcinogenesis, making them a promising source of original anti-tumour medical and chemoprevention preparations (Galasso et al., 2019). Cancer preventive effects of the compounds of marine algae are associated with immunogenic properties (Sansone et al., 2021). Therefore, fucoidan, sulfated polysaccharides (dopolan and supolan), carrageenans and pectins stimulate the work of the complement system, processes of phagocytosis, synthesis of immunoglobulins, mechanisms of cellular defence, particularly production and differentiation of T-lymphocytes and natural killers, increase the level of immunoglobulin A. The advantages of microalgae used for the development of medical preparations are their metabolic plasticity and possibility of their cultivation in photobioreactors, obtaining a larger amount of biomass. Currently, commercial production of microalgae is around 5,000 tonnes of dry mass a year (Abidizadegan et al., 2020). They are recognized as promising objects for scientific developments in the pharmaceutical and biomedical industries, the food industry, in production of biomaterials, biofuel (Balasubramanian et al., 2021; Remize et al., 2021).

The most important role in life of the host organism is played by fungi, bacteria, viruses and microalgae, by providing food, protection, and re-

production. It was determined that many active substances are produced not by marine organisms, but endosymbiotic microorganisms associated with them (Gerwick & Moore, 2012; McCarthy et al., 2019). Compounds exuded by symbionts, such as sterols, alkaloids, peroxides, terpenes, fatty acids, derivatives of aminoacids, cyclic peptides, depsipeptides, polyketides, xanthenes, toxins, bryostatins are highly biologically active. For example, Actinobacteria, especially those of the *Streptomyces* genus, produce around 100 natural products, which provide different types of biological defence to their host organisms. The most productive symbionts are considered Actinobacteria, Proteobacteria, Bacteroidetes, Firmicutes, Cyanobacteria (Zhang et al., 2017; Gavriilidou et al., 2021). Marine associative algae, other than having broadly known medical-preventive and biopharmaceutical values, produce substances that inhibit the growth of pathogenic bacteria and viruses that affect the vital processes of host organisms, including industrially valuable mollusks and fish (Riccio et al., 2020). Marine fungi live in symbiosis with various microbial communities, their biological properties are well known, but the potential of associating organisms remains studied incompletely. Recent surveys of 450 chemical compounds of nudibranchs and symbionts, which are some of the most chemically diverse groups, have revealed their impressive bioactive potential (Avila & Angulo-Preckler, 2020).

To identify the most bioproductive communities and their pharmacological properties, genetic surveys are being carried out (Knobloch et al., 2020). New technologies of growing symbiotic organisms of sponges are being developed for the purposes of cultivation and further obtaining of isolates of the dominant and most productive microbial associates in the pharmaceutical industry (Knobloch et al., 2019). For instance, 1,200 new bioactive compounds were reported to be identified from Ascidiacea, but recent studies have revealed that biologically efficient products are synthesized by Ascidiacea to a lower degree than symbiont microorganisms (Watters, 2018; Dou & Dong, 2019). Corals provide symbiotic co-existence of mollusks, crustaceans, sponges, fishes, worms, viruses, bacteria, algae, fungi; however, symbiotic communities of associating organisms of coral reefs are so far studied insufficiently (Blackall et al., 2015; Kellogg, 2019). Viral, bacterial, fungal associating organisms provide physiological stability of corals and resistance of the system to various stressor effects by producing toxic bioactive compounds, antibiotics, which destroy pathogens through lysis, affecting the composition of holobiont and production of secondary metabolites by symbionts (Roach et al., 2020). Symbiotic communities produce many powerful compounds (carbohydrates, exopolysaccharides, lipids, peptides, alkaloids, polyphenols, steroids, polyketides, terpenoids and zoanthoxanthin), which have cytotoxic, anti-tumour, neuroprotective, antiparasitic, antibacterial effects, and constitute the richest source of new natural compounds with varied chemical structure, high biochemical, pharmacotherapeutic and industrial potentials (Yang et al., 2018; Peter et al., 2019; Madalena et al., 2021).

Antibody–drug conjugates of marine origin with beneficial loads

Against various types of malignant tumours, standard methods of chemotherapy are the only approaches to treatment. Classic medical preparations affect the carcinogenesis through various mechanisms: by neutralizing antigene proteins, blocking their endothelial receptors, inhibiting synthesis of proteins by cancer cells, directly inducing apoptosis of endothelial cells, destroying the tubulin and vascular network of tumours (Pérez-Pérez et al., 2016). However, such preparations damage healthy cells as well, causing the patients to suffer heavy side-effects, and the toxic impact is first of all suffered by the cells of the mucous membrane of the gastrointestinal tract, reproductive and immune systems, and hair. Modern methods of targeted anti-tumour therapy can be aimed at cancer cells. They include the comparatively recently developed system of antibody–drug conjugates, which allow a target impact on malignant tumours, thus making it less harmful for healthy cells.

Antibodies are large molecules of the immune system, which are able to develop specific relationships with the cellular surface of an “alien” object, and eliminate it through complex processes. This natural mechanism, intrinsic in the organism, is a principle of the work of antibody–drug conjugates (or “immune-conjugants”). In clinical practice, monoclonal antibodies demonstrated a large potential and efficiency as new classes of prepa-

rations. An antibody-drug conjugate (ADC) is a three-component molecule that consists of antibody (unit of selective targeting), medical cytotoxic preparations (beneficial loads) and chemical/peptide linker that combines them. The antibody provides conjugant directly to affected cells, interacts with specific tumour markers, protein-antibody expressed only by tumour cells. Then, ADC internalizes, and then, when introduced to the cell, there occurs breakdown of the linker, release of medical agent that suspends mitosis and apoptosis of cancer cells. Therefore, the toxin, strongly bound with the antibody, enters the tumour cell, practically not damaging the healthy tissue.

As beneficial loads, half of the most often used ADCs contain auristatins (monomethyl auristatin A and monomethyl auristatin F), powerful anti-tubulin agents, synthetic analogues of marine dolostatin 10, which are cytotoxic ultrapotent inhibitors of microtubules (Johansson et al., 2017). Monomethyl auristatin E (MMAE, vedotin) is an effective anti-mitotic preparation that inhibits splitting of cells through blocking polymerization of tubulin. MMAE exceeds the cytotoxicity of doxorubicin (adriamycin/rubex) by 100–1000 times. Therefore, it is not used as an individual medical preparation, and is applied as beneficial medical load in the content of ADC. Monomethyl auristatin F (MMAF) is a powerful inhibitor of tubulin polymerase. It is different from MMAE because the residual of norephedrine is replaced by phenylalanine and because of the lower penetrability to the cells. By overcoming internal resistance of the tumour, auristatins increase sensitivity of cells to ionizing emission, which improves the quality of X-ray surveillance of the tumour process and increases the therapeutic efficacy of impenetrable radiation-sensitizing agents during X-ray therapy (Bourillon et al. 2019; Hingorani et al., 2020). Studies of ADC with dolastatins, other than the generally known direct cytotoxic effect, demonstrate such effects as induction of homing of dendritic cells and activation of the system of cellular anti-tumour immunity (Müller et al., 2014). The unique quality of ADC is the antitumour impact combining immune- and chemotherapy in one preparation (Choi et al., 2015). Their efficiency depends on every component separately, as well as their cohe-

rent interaction, which includes many internal and external cellular processes. Nine ADCs have been approved, over 16 have passed the clinical trials, over 60 are being studied at various phases, and numerous research projects on studying and improving the properties and overcoming mechanisms of resistance to them are underway (Greene et al., 2020; Zhao et al., 2020).

Having adapted to variable and not always favourable conditions of existence in the marine environment, marine organisms synthesize many toxic compounds, which are different from biologically active terrestrial analogues. Unlike their synthetic derivatives, they have a more complex chemical structure, thus demonstrating more interesting, and often outstanding chemical properties (Jimenez et al., 2020). Many of the above-mentioned marine organisms produce unique biochemical substances, making them quite promising for the development of new pharmaceutical preparations with multi-target therapeutic effects. Thus, marine organisms produce natural biologically active products, broadly used in many spheres of science, practical medicine and industry.

Currently, 12 preparations are in use obtained from marine organisms, which were approved by the FDA (Food and Drug Administration of the USA) and EMEA (European Medicines Agency – agency dealing with evaluation of medical preparations for their correspondence to the requirements written in the European Pharmacopoeia) and registered as medicinal preparations for therapy of oncological patients (Fludarabine, Cytarabine, Midostaurin, Nelarabine, Eribulin mesylate, Brentuximab vedotin, Trabectedin, Plitidepsin, Enfortumab vedotin, Polatuzumab vedotin, Belantamab mafodotin, Lurbinectedin), a total of 27 compounds are being tested at various phases of clinical trials (Table 1). We used the recent data about the clinical trials from the updating official sources of the EU and USA (www.clinicaltrials.gov; www.clinicaltrialsregister.eu).

Cytotoxic substances, trials of which were completed or stopped at the intermediate phases, demonstrated their anti-tumour effects. Studies of their therapeutic properties are likely to be continued against various types of tumours and other diseases (Table 2).

Table 1
Anti-tumour preparations from marine organisms currently undergoing various phases of clinical trials

Name of drug/ Company	Marine organism/ chemical class	Purpose, target	Mechanism of action	Reference
Preparations approved for use and at various phases of clinical trials against different types of cancer				
Fludarabine (Vidarabine, Fludara, F-ara-AMP, Ad/ PNP-F-araAMP/ PNP)/ Therapeutics, Inc.	Fungi/ Nucleoside	Leukoses, lymphomas	Cytostatic of the group of purine antagonists, inhibitor of key DNA enzymes, apoptosis inductor	Lowe et al., 2018; Barreca et al., 2020; Cooper et al., 2020.
Cytarabine (ARA-C, Cytozar-U [®] , DepoCyt [®])/ Pfizer	Fungi/ Nucleoside	Leukoses	Inhibitor of DNA-polymerase, damages DNA in S-phase of cellular cycle	Salehi et al., 2019; Frankel et al., 2020.
Nelarabine (Arranon)/ Washington University School of Medicine	Fungi/ Nucleoside	Leukoses, lymphomas	Purine antimetabolite, accumulates mostly in T-cells, mechanism of action is similar to cytarabine	Kadia et al., 2017; Barreca et al., 2020; Dunsmore et al., 2020.
Midostaurin (PKC 412)/ Novartis Pharmaceuticals, Stichting Hemato-Oncologie voor Volwassenen Nederland	Ascidacea, Actinobacteria / Indolocarbazole	Acute myelogenous leukemia, hematologic cancer	Multi-target inhibitor of protein kinase 3 (FLT 3), active against oncogenic CD 135	Barreca et al., 2020; Orgueira et al., 2020; Morell et al., 2021.
Eribulin mesylate (Halichondrin B, E7389, Halaven [®])/ Eisai Inc.	Fungi/ Macrolide	Refractory solid tumours; Ewing's sarcoma, metastatic mammary gland cancer	Non-taxane inhibitor of dynamics of microtubules with high anti-mitotic activity	Barroso-Sousa et al., 2020; Tolaney et al., 2020; Yuan et al., 2021.
Brentuximab vedotin (SGN 35, Adcetric [®])/ Seattle Genetics	Mollusks, cyanobacteria / ADC with MMAE	T-cellular lymphomas, Hodgkin lymphoma	First target ADC-preparation. Targeted at CD30-positive tumour cells, microtubules	Chen et al., 2020; Straus et al., 2020.
Trabectedin (E7-743, Yondelis [®])/ Pharmamar	Ascidacea / Alkaloid	Progressive liposarcoma, metastatic sarcomas of the soft tissues	Pleiotropic mechanism of action, has effect on the key cellular processes and micro-environment of tumour	Miwa et al., 2019; Kobayashi et al., 2020; Martínez-Trufero et al., 2021.
Plitidepsin (dehydrodidemnin B, Aplidin [®])/ PharmaMar	Ascidacea / Cyclodepsipeptide	Medulloblastoma, leukoses and liposarcomas; MCF-7	Specifically binds with eEF1A2, activates RAC1 and phosphorylation of JNK1, induces apoptosis depending on the type of cell and dose. Inhibitor of microtubule assembly. Regulates expression of growth factor gene of the blood vessels of the endothelium and blocks its secretion	Popov, 2006; Xu et al., 2012; Newman & Cragg, 2014; Alonso-Álvarez et al., 2017; Xing et al., 2017; Martínez Andrade et al., 2018; Pereira et al., 2019; Losada et al., 2020.
Enfortumab vedotin (AGS-22MSE)/ Agensys, Seattle Genetics, Astellas Pharma	Mollusks, cyanobacteria / ADC with MMAE	Multiple solid tumours, metastatic cancers of the urinary system and the mammary glands	The first and the only agent aimed at nectin-4, molecule of cellular adhesion, which expresses on many solid tumours	Newman, 2019; Pereira, 2019; Hanna, 2020.

Name of drug/ Company	Marine organism/ chemical class	Purpose, target	Mechanism of action	Reference
Polatuzumab vedotin (Polivy™, DCDS4501A, RG7596)/ Genentech, Roche	Mollusks, cyanobacteria/ ADC with MMAE	Recurrent or refractory diffusive large B- cell lymphoma	Selectively binds with CD79b on the surface of B-cells, inhibits polymerization of tubulin, suspends phase G2 / M and apoptosis of tumour cells	Wang, 2017; Nejadmog- haddam et al., 2019; Pereira et al., 2019; Amaya et al., 2020; Choi & Diefenbach, 2020.
Belantamab mafodotin (GSK2857916, Blenrep™)/ GlaxoSmithKline	Mollusks, cyanobacteria/ ADC with MMAE	Recurrent and refractory multiple myeloma	Afucosylated antibody IgG1 aimed at antigen maturation of B-cells (BCMA)	Pereira et al., 2019; Tzogani et al., 2020; Musaimi et al., 2021.
Lurbinectedin (LY-01017, PM-01183, Zepsyre, Zepzelca™)/ PharmaMar	Ascidacea / Alkaloid	Sarcomas of the soft tis- sues, chronic lymphocytic leukemia. Orphan drug for ovarian cancer, small –cell lung cancer	Inhibits the processes of oncogenic transcription, covalently binding with DNA in the tumor tissues, stimulates anti-tumor immunity, directly affects the micro-environment of tumours	Popov, 2006; Takahashi et al., 2016; Belgiovine et al., 2017; Calvo et al., 2017; Martínez Andrade, 2018; Kauffmann-Guerre- ro, 2020; Markham, 2020.
Phase III				
Plinabulin (NPI-2358)/ Nereus Pharmaceutical	Marine fungi / Diketopiperazine	Multiple myeloma, adenocarcinoma of the large intestine, prostate, the mammary glands	Blocks polymerization of tubulin through unique mechanism, leading to multi-factor effects, intensified immune-oncologic response and disruption of blood support of tumour	Singh et al., 2011; Martínez Andrade et al., 2018; Pereira, 2019; Jimenez, 2020; Tonra et al., 2020.
Marizomib (Salinosporamide A, NPI 0052)/ Nereus Pharmaceutical, Celgene, Triphase	Actinomycetales / γ-lactam-β-lactone	Glioblastoma, carcinoma of large intestine, CNS tumour, melanoma, non- small-cell lung cancer, mammary glands cancer	The only inhibitor of activity of proteasomes, which can overcome blood–brain barrier. Covalently modifies the residues of teonin, active site of 20S- proteasome	Martins et al., 2014; Jensen et al., 2015; Pérez- Pérez et al., 2016; Pereira et al., 2019; Roth et al., 2020; Sherman & Li, 2020.
Phases II/III				
Depatuxizumab mafodotin (depatux-m, ABT-414, ABT 806)/ Abbvie	Mollusks, cyanobacteria/ ADC with MMAE	Squamous cell cancer of the lungs, glioblastoma multiforme	Binds EGFR epitope on the surface of cell, interna- lizes and releases cys-mcMMAF (cys-mafodotin), binds with the network of microtubules, suspending the proliferation of tumour cells	Pereira et al., 2019; Biteghe et al., 2020; Van Den Bent et al., 2020.
Phase II				
Oligo-fucoidan / Hi-Q Marine Biotech International, Ltd.	Brown marine algae / Polysaccharide	Metastatic colorectal cancer, hepatocellular carcinoma, mammary glands cancer, lung cancer	Has effect on receptor of transformation growth factor (TGF-β), inhibits epithelial-mesenchymal transition in tumour cells	Tsai et al., 2017; Lin et al., 2020; Miyata et al., 2020.
Tisotumab vedotin (Hu Max ^R -TF- ADC, TF-011-MMAE)/ Genmab, Seattle Genetics	Mollusks / ADC with MMAE	Metastatic cervical cancer, endometrial cancer, bladder cancer, prostate cancer, eso- phagus cancer, squamous cell carcinoma of the head and neck	The first ADC in its class, which contains human tissue factor (TF)-specific monoclonal antibody. Inhibitor of microtubules, immune-toxin	De Bono et al., 2019; Newman, 2019; Pereira et al., 2019; Hong et al., 2020.
AGS-16C3F (AGS-16M8F)/ AgenYS Inc, Astellas Farma Inc.	Mollusks, cyanobacteria / ADC with MMAE	Carcinoma of the liver, metastatic hepatocellular cancer	Inhibitor of tubulin polymerase, tubulin, mytosis; apoptosis stimulator. Targets phosphodiester 3, ectonucleotide pyrophosphatase (ENPP3)	Newman & Cragg, 2017; Gogineni & Hamann, 2018; Pereira et al., 2019; Koll- mannsberger et al., 2021.
Telisotuzumab vedotin (ABBV-399) / ABBVie	Mollusks, cyanobacteria / ADC with MMAE	Recurring and stage IV of lung cancer, advanced cases of cancer	The first ADC in its class that contains humanized monoclonal antibody ADT 700. Aimed at c-Met expressing tumour cells	Strickler et al., 2018; Newman, 2019; Pereira et al., 2019.
Dolastatin 10 and 15 / Seattle Genetics	Mollusks, cyanobacteria / Linear pentapeptide	Mammary cancer, cancers of the large intestine, the liver, solid tumours and some leukoses	Obstructs formation of tubulin, induces apoptosis and phosphorylation of Bcl-2 in some types of malignant cells. Suspends cellular cycle in phase G2-M	Perez et al., 2005; Martínez Andrade et al., 2018; Yang et al., 2019; Ratnayake et al., 2020.
Phases I/II				
KRN 7000 (Agelasphin derivate) / Shanghai Public Health Clinical Center	Fungi / α-Galactosylceramide	Cancers of the lungs, stomach, kidneys, liver	Inductor of stable proliferation and production of interleukins of iNKT cells	Fuji et al., 2000; Anderson et al., 2013; Hartampf et al., 2020; Washah et al., 2020.
Cimtuzumab vedotin (UC961ADC3) / UC San Diego	Various / ADC with MMAE	Solid tumours, B-cellular lymphocytic leukemia, mammary cancer	Targets epitope of ROR1. Competative inhibitor of binding ligand WNT, interrupts signal cascade associated with effects of ROR1	Choi et al., 2015; Choi et al., 2018; Menck et al., 2021.
XMT 1536 (Upifitamab nlsodotin) / Mersana Therapeutics, IQVIA Biotech	Mollusks, cyanobacteria / ADC Dolaflexin with MMAE	Platinum-resistant ovarian cancer, metastatic non-small- cell lung cancer, tumours that express NaPi2b	Novel technology of ADC, contains higher concentration of medical antibody and novel auristan F- hydroxypropylamine (AF-HPA). Targeted at Her2, NaPi2b	Manzano & Ocaña, 2020; Yurkovetskiy et al., 2021.
MORAb-202 / Eisai Inc.	Fungi / ADC (contains farletuzumab and eribulin)	Solid tumours	Humanized antibody farletuzumab against folate receptor FRα, beneficial load – eribulin MTA (derivative of halichondrin B). Inhibitor of microtubules	Cheng et al., 2018; Matsunaga et al., 2021.
Soblidotin (TZT-1027, derivate Dolastatin 10) / Aska Pharmaceuticals	Mollusks, cyanobacteria / Linear peptide	Broad range of activity against xenotransplantation of human tumours	Inhibits polymerization of tubulin, suspends division of tumour cells in very low concentrations, suppresses angiogenesis, inhibits processes of mytosis and angiogenesis on the models of progressing tumour	Akashi et al., 2007; Martins et al., 2014; Frau et al., 2019.
Plocabulin (PM 060184, PM 184) / Pharma Mar	Fungi / Polyketide	Mammary gland tumours, colorectal cancer, advanced solid tumours	Inhibits tubulin polymerization, processes of mytosis. Strong inhibitor of microtubules with unique molecular mechanism	Newman & Cragg, 2014; Prota et al., 2014; Miller et al., 2018; Pereira et al., 2019; Jimenez et al., 2020.

Name of drug/ Company	Marine organism/ chemical class	Purpose, target	Mechanism of action	Reference
Zalypsis (PM 00104, PM 10450) / Pharma Mar	Mollusks / Alkaloid	Cervical cancer, endometrium cancer; Ewing's sarcoma, leukoses, lymphomas, solid tumours, multiple myeloma, urogenital cancer	Inhibits proteins of cellular cycle, transcription factors; DNA-binding protein modulator	Newman & Cragg, 2014; Petek, 2014; Ocio et al., 2016; López-Iglesias, 2017; Ruiz-Torres et al., 2017.
Ladiratuzumab vedotin (SGN-LIV1A, SLC39A6, ZIP6) / Seattle Genetic Inc.	Mollusks, cyanobacteria / ADC with MMAE	Metastatic cancer of mammary gland, melanoma, prostate cancer, cancer of the ovaries and the womb	Aimed at transmembrane protein LIV-1 (SLC39A6). Splits proteases, inhibits tubulin polymerase, mytosis processes, increases apoptosis	Boni et al., 2019; Newman, 2019; Pereira et al., 2019.
Kahalalide F / PharmaMar, Hawaii University	Mollusks, cyanobacteria / Cyclic dipeptide	Cancers of mammary gland, prostate, neuroblastoma, osteosarcoma	Inhibits expression of growth factor TGF- α , signal pathways of PBK-AKT in cellular lines of mammary cancer SKBR3 and BT474	Shilabin & Hamann, 2011; Martins et al., 2014; Leea et al., 2017; Rosa et al., 2019.
RC-48 (Disitamab vedotin, RC 480-ADC) / RemGen	Various / Recombinatory ADC anti- <i>Her2</i> with MMAE	Mammary cancer, lung cancer, metastatic urothelial cancer, stomach cancer	Targets epidermal growth factor, receptor protein tyrosine kinases erbB-2, EGFR2, HER2, HER-2, p185c-erbB2, NEU, CD340	Newman, 2019; Li et al., 2020; Sheng et al., 2021.
CAB-ROR2-ADC (BA-3021, CAB-AXL-ADC) / BioAlta, LLC	Mollusks, cyanobacteria / ADC with CAB, anti ROR-2 with unknown cytotoxic agent	Sarcoma of the soft tissues, non-small-cell lung cancer, triple-negative breast cancer, pancreatic cancer, melanoma	Patented technology. CAB-antibody selectively binds with ROR2-expressing cancer cells, thereby achieving maximum effect while having minimum toxicity	Newman, 2019; Pereira et al., 2019; Dyshlovoy & Honecker, 2020; Menck et al., 2021.
CX-2029 / AbbVie, CytomX Therapeutics	Various / ADC with MMAE	Cancer of the head and neck, non-small-cell lung cancer, cancer of the pancreas, diffusive large-cell lymphoma, inoperable solid tumours, B-cellular lymphomas	System uses Probody ^(TM) preparation aimed at CD71. Has impact on cancer targets that are inaccessible for regular ADC	Polu & Lowman, 2014; Newman, 2019; Autio et al., 2020.
Enapotamab vedotin (HuMax-AXL-107) / GenMab	Mollusks / Axl-specific ADC with MMAE	Ovary cancer, cervical cancer, endometrial cancer, pancreatic cancer, lung cancer, melanoma	Experimental chemoimmunoconjugate aimed at receptor tyrosine kinase Axl, blocks polymerization of tubulin in tumour cell, induces apoptosis of cancer cells	Koopman et al., 2019; Newman, 2019.
W0101 / Pierre Fabre Medicament	Mollusks, cyanobacteria / ADC with MMAE	Solid metastatic tumours	Contains humanized antibody hz208F2-4, specifically binds with receptor IGF-1R, blocks polymerization of tubulin	Akla et al., 2020; Dyshlovoy & Honecker, 2020.
Phase I				
ZW-49 / Zymeworks Inc.	Mollusks, cyanobacteria / Biospecific ADC with MMAE	Metastatic tumours, expressing Her2	Aimed at Her2 on tumour cells	Boni, 2020; Tolcher, 2020.
ARX 788 / Ambrx, Inc	Mollusks, cyanobacteria / ADC with MMAE	Her2-positive tumours of the stomach, breast cancer	Site-specific ADC of new generation, uses unique technology of conjugation and non-splittable Amberstatin (AS269). Active against tumour cells with high expression of Her2.	Skidmore et al., 2020; Barok et al., 2021.
ALT-P7 / Alteogen, Inc.	Mollusks, cyanobacteria / ADC with MMAE	Her2-positive breast cancer	Comprises trastuzumab biobetter HM2 and MMAE	Rinnerthaler et al., 2019; Luque-Bolivar et al., 2020; Park et al., 2020.
PF-06804103 / Pfizer	Mollusks, cyanobacteria / ADC with Aur 0101	Mammary gland cancer, stomach cancer	Variant of ADC which contains monoclonal antibody anti-Her2, conjugated splittable linker with cytotoxic agent Aur 0101. Aimed at Her2,	Graziani et al., 2020; Meric-Bemstam, 2020.
PSMA-ADC / Seattle Genetics, Roots Analysis, Progenics	Mollusks, cyanobacteria / ADC with MMAE	Cells of prostate cancer, glioblastoma multiforme	Intended for selective binding of PSMA-expressing cells, inhibits proliferation of cells, ruining cytoskeleton	Wang et al., 2011; Newman, 2019; Petylak et al., 2020.

Table 2
Anti-tumour substances, trials of which were completed at different phases of clinical studies

Name of drug/ Company	Marine organism/ chemical class	Purpose, target	Mechanism of action	References	Phase of study
Keyhole Limpet Hemocyanin (KLH) / Intracel, Rockville, Immucothell [®] , Biosyn Arzneimittel-GmbH, Fellbach, Calbiochem	Mollusks / Glycoprotein	Metastatic cancer of mammary gland, bladder cancer; ovary cancer, cancers of the pancreas, prostate, recurring glioblastoma, neuroblastoma, non-Hodgkin lymphoma, skin melanoma	Modulates processes of synthesis of inflammatory and pro-inflammatory mediators, increases early and late apoptotic activity in MCF-7 cells, reduces late apoptotic activity in ZR75-1 cells	Lammers et al., 2012; Wimmers et al., 2017; Newman, 2019; Román et al., 2019.	I/III
Iladatuzumab vedotin (DCDS0780A, RO7032005) / Hoffmann-La Roche	Various / ADC with MMAE	Recurring or refractory B-cell lymphoma	Targets CD-79A-cells	Liersch et al., 2005; Sahlmann et al., 2017.	II
Indusatamab Vedotin (MLN-0264, 5F9veMMAE, TAK-264) / Seattle Genetics	Mollusks, cyanobacteria / ADC with MMAE	Progressing pancreatic adenocarcinoma, tumours of the gastro-intestinal tract, which express guanylate cyclase 2C	Aimed at guanylate cyclase 2C	Newman & Cragg, 2014; Almhanna et al., 2017; Gogineni & Hamann, 2018.	I/II
Pinatuzumab vedotin (DCDT2980S, FCU2703) / Genentech, Roche	Mollusks, cyanobacteria / ADC with MMAE	Non-Hodgkin lymphoma, leukosis	Stimulates processes of apoptosis, inhibits processes of mytosis, polymerisation of tubulin, targets CD22	Forero-Torres et al., 2016; Advani et al., 2017; Morschhauser et al., 2019; Yu et al., 2021.	I/II

Name of drug / Company	Marine organism / chemical class	Purpose, target	Mechanism of action	References	Phase of study
Glembatumumab vedotin (CDX-011, CR011) / Seattle Genetics, Celldex Therapeutics	Mollusks, cyanobacteria / ADC with MMAE	Squamous cell lung cancer, melanoma, triple negative cancer of the mammary gland, recurring osteocarcinoma, uveal melanoma	Induces partial or complete regression of cancer cells that express GPNMB; inhibits the set of microtubules	Ott et al., 2019; Patrick et al., 2019; Pereira et al., 2019; Wolska-Washer & Robak, 2019; Hasanov et al., 2020; Kaštelan et al., 2020.	I/II
Tasidotin (ILX-651, derivate Dolastatin 15) / Genzyme Corporation	Mollusks / Pentapeptide	Erythroid leukosis, ovary cancer, carcinoma of the large intestine, cells of mammary cancer, lung carcinoma, melanoma	Inhibits processes of proliferation, mytosis, polymerization of tubulin in microtubules	Ray et al., 2007; Martins et al., 2014; Frau et al., 2019.	I/II
PF-06263507 (A1-mcMMAF) / Pfizer	Mollusks, cyanobacteria / ADC with MMAE	Progressing solid tumours, leukoses	Fragment of antibody selectively binds with 5T4-expressing cells. Inhibits polymerization of tubulin, leads to suspension of phase G2 / M and apoptosis of tumour cells	Forero-Torres et al., 2016; Shapiro et al., 2017; Gogineni & Hamann 2018; Newman, 2019.	I
DMUC-5754A (Sofituzumab vedotin, RG-7458) / Hoffmann-La Roche Ltd, Genentech	Mollusks, cyanobacteria / ADC with MMAE	Ovary and pancreatic cancers	Contains humanized monoclonal antibody against MUC16. Inhibitor of tubulin polymerase, apoptosis stimulator	Newman & Cragg, 2014; Liu et al., 2016; Gogineni & Hamann, 2018.	I
Elisidepsin (PM02734, Irvalec; 15b) / Pharma Mar	Mollusk / Depsipeptide	Solid tumours, metastatic cancer of the esophagus, stomach cancer, squamous cell lung cancer	Self-organizes and modifies lipid constituents of plasmatic membrane of tumour cells, increases penetrability of cells, induces apoptosis	Petty et al., 2016; Kang et al., 2018; Van Andel et al., 2018; Chakraborty & Joy, 2020.	I
Bryostatin-1 / National Cancer Institute (USA)	Bryozoa / Macrocyclic lactone	Melanoma, lymphoma, ovary carcinoma, liver carcinoma, leukosis. Orphan drug in combination with paclitaxel during esophagus cancer	Selective inhibitor of non-typic isophorm of protein kinase C. Induces synthesis of cytotoxins, immune-stimulator	Popov, 2006; Kim & Guan, 2015; Ciavatta et al., 2020; Raghuvanshi et al., 2020.	I
DNIB-0600A (Lifastuzumab vedotin, RG-7599, GTPL8405) / Genentech Inc.	Mollusks, cyanobacteria / ADC with MMAE	Non-small-cell lung cancer, platinum-resistant ovarian cancer	Targets NaPi2b epitope, blocks polymerization of tubulin	Newman & Cragg, 2017; Gogineni & Hamann, 2018; Gerber et al., 2020; Moore et al., 2020.	I
DMOT-4039A (RG-7600) / Genentech Inc.	Mollusks, cyanobacteria / ADC with MMAE	Inoperable pancreatic or platinum-resistant ovarian cancer	Contains humanized IgG1-anti mesothelin mAb h7D9.v3. Destroys the microtubule network, induces apoptosis	Newman & Cragg, 2014; Weekes et al., 2016; Gogineni & Hamann, 2018.	I
DEDN-6526A (RG-7636) / Genentech, Seattle Genetics	Mollusks, cyanobacteria / ADC with MMAE	Inoperable melanoma	Anti-microtubule agent, inhibitor of tubuline-polymerase, mitosis, apoptosis inducer	Newman & Cragg, 2014; Gogineni & Hamann, 2018; Nejadmoghaddam et al., 2019.	I
Vandortuzumab vedotin (DSTP-3086S, RG-7450) / Genentech (Roche)	Mollusks, cyanobacteria / ADC with MMAE	Metastatic prostate cancer	Modified humanized antibody against STEAP1 IgG1, bond with MMAE through Me-VC-PABC. Aims at epithelial prostate antigene	Newman & Cragg, 2014; Van Andel et al., 2018.	I
Sirtratumab vedotin (AGS-15E, AGS-15ME) / Agensys, Seattle Genetics	Mollusks, cyanobacteria / ADC with MMAE	Cancers of the bladder, lungs, mammary glands, glioblastoma	The first and the only agent aimed at transmembrane protein SLITRK6. Effectively binds with target cells, induces apoptosis	Hofland, 2016; Petrylak et al., 2016; Pereira et al., 2019.	I
AGS 67E / Agensys, Inc., Astellas Pharma	Mollusks, cyanobacteria / ADC with MMAE	Aims at CD37. Refractory lymphocytic leukemia, non-Hodgkin lymphoma	Targeted at CD37. Has high cytotoxicity, induces apoptosis and changes in cellular cycle in many cellular lines	Pereira et al., 2015; Newman et al., 2017; Pereira et al., 2019.	I
Cofetuzumab pelidotin (PF-06647020) / Pfizer	Mollusks / ADC with auristatin (anti-PKT7)	Solid tumours	Mitosis inhibitor, apoptosis stimulator, inhibitor of tubuline polymerisation	Kato, 2017; Newman, 2019.	I
PF-06380101 (Q8020AX34E) / Pfizer	Mollusks, cyanobacteria / ADC with MMAE	Solid tumours, triple negative and metastatic breast cancer	Analogue of dolastatin 10, inhibitor of polymerization of tubulin	Rago et al., 2017; Pereira et al., 2019.	I
ABBV-085 (Samrotamab vedotin) / AbbVie, Inc.	Various / Anti-huLRRC15 ADC	Solid tumours, undifferentiated pleoform sarcoma, squamous cell cancer of the head and neck, mammary gland cancer	Aims at LRRC15 in the micro-environment of tumour	Madema et al., 2014; Purcell et al., 2018; Pereira et al., 2019; Hingorani et al., 2021.	I
XMT 1522 (TAK-522) / Mersana Therapeutics	Various / ADC with MMAE-HPA	Cancers of the stomach, lungs, mammary glands	Anti- Her2-antibody-medical preparation	Hamilton et al., 2018; Le Joncour et al., 2019.	I
Hemiasterlin E7974 / Eisai Inc.	Fungi / Linear tripeptide	Solid tumours	In vitro inhibitor of polymerization of tubulin, proliferation of broad range of cancer cells, overcomes the resistance against other anti-tubulin agents	Rocha-Lima et al., 2012; Marchetti et al., 2016; Won et al., 2019; Zhang et al., 2021.	I
BAY 79-4620 (3e9MMAE) / Seattle Genetics	Mollusks, cyanobacteria / ADC with MMAE	Progressing solid tumours, CA9-positive stomach cancer	Targets carbonic anhydrase IX (CA9) of human, inhibitor of tubulin polymerization	Francisco et al., 2003; Petrul et al., 2012	I
Denintuzumab mafodotin (SGN-CD19A, SGN-19A / BU12-491) / Seattle Genetics	Mollusks, cyanobacteria / ADC with MMAE	CD19-positive acute lymphoblastic leukemia, B-cell non-Hodgkin lymphoma	Humanized anti-CD19-antibody, anti-microtubular agent	Shah et al., 2017; Jones et al., 2019; Newman, 2019; Pereira et al., 2019; Mc Nemey & Teachey, 2021.	I
SGN-75 (Vorse-tuzumab mafodotin) / Seattle Genetics	Mollusks, cyanobacteria / ADC with MMAE	Recurring and refractory non-Hodgkin lymphoma, hepatocellular adenocarcinoma	Induces apoptosis of tumour cells, inhibits proliferation of tumour cells that overexpress CD70	Tannir et al., 2014; Pereira et al., 2019	I

Trials of biopharmaceutical production

Preparation of a pharmaceutical product starting from the moment of discovering the biochemical potential of a substance to the industrial production of drug includes laboratory, pre-clinical and clinical trials. The pharmaceutical company determines the chemical and molecular formula of the preparation, develops the form of the production, and then conducts pre-clinical trials. The pre-clinical stage includes many biological, microbiological, pharmacological, chemical, physical and toxicological studies on cellular lines or laboratory animals. The main goal of pre-clinical trials of preparation is obtaining evidences of the efficacy and safety of the preparation. By the end of pre-clinical trials of preparation, its action is tested in at least three stages on people who gave their voluntary consent. Preparation goes to the next stage only after it has proved to demonstrate satisfactory results in the previous one.

Clinical trials at phase I are carried out on 10–15 healthy volunteers or terminally ill patients with their agreement. The goal of the trials is determining the pharmacokinetic and pharmacodynamic parameters, parameters of toxicity, preliminary evaluation of safety of and tolerance to the preparation. Also, the trials examine the parameters of absorption, processes of metabolism, distribution and excretion in the organism, and determine the preferable form of application and safe level of dose. Clinical surveys of the first phase last several weeks to one year.

The goals of trials at phase II entail determination of optimum dosage and selecting the scheme of introduction of the preparation. At this stage, the number of tested patients increases up to 300 patients, the details of dosages, mechanisms of action, side-effects and the methods of their minimization are tested.

Clinical trials at phase III are randomizing controllable multi-center surveys involving a large group of volunteer patients – 1,000 and more. The goals of phase III are to confirm the preliminary data obtained during the previous studies and compare the actions of the preparations to standard therapy regarding particular oncologic disease. At this stage, therapeutic efficiency of the preparation is studied depending on the dose. If, by the end of the clinical studies at phase III, the positive effect of treatment remains, the patients continue to receive this drug until stable remission. Surveys at phase III may be continued if the sponsoring company wishes to broaden the drug's to-use indications, and are classified as phase IIIB.

Interestingly, in cancer patients with late stages of diseases, anti-tumour natural compounds tested in randomized conditions as monopreparations or combined with other chemotherapeutic preparations demonstrated longer clinical response compared with the traditional chemopreparations (Blay et al., 2015; El Bairi et al., 2017; Teplinsky & Herzog, 2017).

Phase IV consists of post-registration clinical trials. They are aimed at collecting data on certain criteria: treatment periods, interaction of new preparation with other medical preparations or food products; analysis of use among patients of various age groups, economic parameters, remote results of treatment, and also collecting additional data on the safety and efficacy of the preparation on the basis of large groups of patients over a long period. During the trials, there may occur a problem of high toxicity and medical resistance, and therefore the evaluation of the effectiveness of clinical surveys of preparations on people often remains limited (Eastman, 2017; El Bairi et al., 2017). The process of preparing a pharmaceutical preparation lasts 10–15 years and costs millions of dollars, and at the same time, less than 12% of potential drugs are ultimately allowed for use. If, over the course of clinical studies, rare but dangerous unsatisfactory processes are found, the preparation is withdrawn from sale.

Scientists who are developing natural marine medical products isolate only several milligrams of promising compounds of new structure. Preliminary in vitro screening on the cancer cell lines requires a small amount of pure compounds. Studies on animals require around 100 mg, and clinical trials – up to several hundreds of grams, but kilograms are needed for its production as a pharmaceutical preparation (Newman, 2016). Biologically active substances from marine organisms are not always available in the required amount. Therefore, for many products obtained from hydrobionts, the only possible way to solve this problem is believed to be chemical synthesis. This method, other than production of the necessary amount of a certain substance, gives an additional advantage – obtaining valuable intermediate compounds and their analogues, which would later

be used in further studies. Chemical synthesis also includes the development of expensive derivatives with more manageable, less complex, properties. For example, production of kahalalide F for clinical trials was developed using the methods of chemistry of solid-phase peptide synthesis, resulting in preparation of over 150 its analogues (Gao & Hamann, 2011). Synthetic methods developed to obtain dolastatins led to emergence of new intermediate substances, such as auristatins, broadly used in contemporary antibody-drug conjugates (Cragg et al., 2012; Newman & Cragg, 2014; Newman & Cragg, 2017). Use of new technologies of aquaculture and profound knowledge in the sphere of genomics and biotechnology allow a synthesis of analogues of natural marine products through chemical synthesis on industrial scales.

Perspectives of using cytotoxic compounds of marine origin in oncology and new biomedical technologies

A great role in the emergence and development of tumour diseases is played by infectious agents (Pimenoff et al., 2019). In 2018, there were diagnosed 2.2 M cases of oncological diseases associated with infectious origin, which accounted for almost 13% of all cases of cancer (De Martel et al., 2020). There is an increasing number of studies confirming high risk of infection and severe course of COVID-19 in cancer patients (He et al., 2021; Li et al., 2021; Tian et al., 2021). Therefore, there is a sharp need to combat infectious triggers of carcinogenesis, which would allow a decrease in the level of morbidity and mortality. Cytotoxic substances of marine organisms, having unique chemical structure, anti-cancer, antiviral, immune-modulating, neuro-protective, antibacterial and many other effects, can make a systemic multi-target impact on cancer cells, as well as infectious agents (Fitton et al., 2020; Gentile et al., 2021; Tagliatalata-Scafati, 2021). Accordingly, a drug of marine origin Plitidepsin (Aplidin®), used to treat tumour diseases, in vitro studies displayed 27.5 times the antiviral activity of remdesivir, the only officially FDA-approved antiviral preparation to treat patients with SARS-Cov-2, and had lower toxicity (White et al., 2021). Studies revealed that along with Plitidepsin, such preparations as Eribulin mesylate and Trabectedin, having properties of inhibitors of SARS-Cov-2 protease, significantly reduce replication of the virus, and therefore the extent of severity of viral infection in cancer patients (Kalhotra et al., 2021). The marine organisms are known to produce antiviral compounds against many other pathogenic viruses, such as HIV, HSV, HHV, influenza A, smallpox virus, SRV-2, HAV, HBV, HCV; EBV, enterovirus, HCMV, JEV, TMV, PrV, WSSV, MS2, CHIKV, OsHV, SINV, TBE, PRRSV, EV-71, FIPV, MHV, BVDV, KHV, WEEV). Nonetheless, there is currently known only one compound of marine origin with antiviral activity against virus of herpes simplex and Varicella zoster – Vidarabin, used in medicine, and another one – Griffithsin, which is undergoing clinical tests against HIV (Riccio et al., 2020).

Drugs of marine origin are used to treat patients with bronchial asthma, Alzheimer's disease, hypertonic disease, with disorders in the processes of blood circulation, autoimmune diseases, pain syndromes, etc. Other than their direct purpose, they may be used for therapy with combined pathology in cancer patients, which would likely reduce drug load on patients, significantly optimize time and financial costs on conducting pre-clinical and clinical trials at early phases.

During the tests, it was found that many bioactive substances of marine origin have additive and synergic effects when combined with traditional anti-tumour preparations. Therefore, Trabectedin (marine alkaloid isolated from *Ecteinascidia turbinata* tunicate), by functioning as a DNA intercalator, coupled with vincristine increases therapeutic effect during treatment of sarcomas of the soft tissues. This allows doses of applied anti-tumour drugs to be decreased, thereby decreasing their toxicity and improving therapeutic index. Likewise, combination therapy may prevent drug-resistance, which significantly limits the traditional anti-tumour medical preparations (Calcabrini et al., 2017).

Contemporary medicine is oriented at application of target methods of cancer therapy, including molecular, cellular, gene therapies and preventive measures, antibody-drug conjugates, nanoparticles of biopolymers, metals, polymeric micelles and other nanoparticles (Liu et al., 2021). Antibody-drug conjugates are a separate class of immune-chemotherapy preparations. Substances isolated from marine organisms (or their synthe-

tic analogues) are considered to be promising beneficial loads for future ADC: hemiasterlin, taltobulin, cemadotin, cryptoficine, discodermolide (Ponziani et al., 2020). New knowledge of the carcinogenesis processes and successes of gene engineering led to development of bispecific antibodies (bsAbs) that have an effect on two targets of carcinogenesis – alter the processes of cellular signal transmission and suspend further growth and metastasis of tumours (Liu et al., 2021). Unlike regular chemotherapeutic drugs, antibody-drug conjugates are a promising and most dynamically developing class of drugs, and have broad therapeutic range due to effective and specific transport of drug to antigen-expressing tumour cells (Mukherjee et al., 2019; Khongorzul et al., 2020). The FDA currently allow nine of them to be used, and over 80 of them, which are aimed at over 50 various antibodies, are at different phases of 600 clinical trials (Boni, et al., 2020, Barok et al., 2021). Despite the high efficiency and promising character of ADCs of the last generation, their synthesis is associated with certain difficulties such as humanization of antibodies, complexity of the processes of modification and conjugation with beneficial load. A number of studies suggest solving these problems by using aptamers, siRNA and DNA-lygands in the content of the conjugants (ApTDC, ASO) (Roberts, 2020). Unlike antibodies, aptamers require no humanization, are easily synthesized and modifiable. In a recent study, E3 aptamer-drug conjugates with beneficial loads MMAE and MMAF (derivatives of marine peptide dolastatin 10) exerted high anti-tumour activity towards many lines of tumour cells (Gray et al., 2020). To improve pharmacokinetics, bioactivity and rates of release of oncological preparations, there are studies underway oriented at developing ADCs of next generation, using site-specific conjugation, changes in the amount and position of beneficial loads, separate particles of completely humanized antibodies.

Numerous studies are currently being conducted dealing with the efficiency of cancer gene therapy, 60% of studies in the sphere of genetic medicine are conducted specifically in oncology (Stuijvenberga et al., 2020). As known, mutations of somatic cells are essential in emergence of tumours and development of medical resistance. Therefore, one of the promising directions in oncology is considered to be gene therapy. Genome DNA is the main target for natural anti-tumour therapeutic preparations (Van Stuijvenberg, 2020). Development of genetic technologies also led to the understanding of critical importance of RNA-influenced regulation of carcinogenesis in conditions of multiple tumours. Thus, the technology of RNA-influenced gene inhibition is considered promising, which demonstrated high efficiency in trials on multiple malignant tumours. RNA-therapeutic technologies in combination with immune- and chemotherapy inhibit several pathways of carcinogenesis at the same time, including overexpression of genes that modulates immune-enzymic system, thus arresting the growth of tumours, process of metastasis and overcoming chemo-resistance (Khan et al., 2021). Gene therapy of cancer involves use of viruses, immune-liposomes that contain stem cells, including autological cells, and also antibodies, nanoparticles of bioactive compounds. At the same time, activation of the pro-drug occurs directly in tumour cells, thereby preventing systemic complications. As active agents, gene therapy successfully uses preparations from marine organisms. Therefore, high efficacy at phase I of the trials was demonstrated by combined use of gemcitabine and siG12D-LODE™ (miniature biodegradable implant based on small interfering RNA, which is aimed specifically at KRAS oncogene) to treat locally advanced pancreatic cancer (Golan et al., 2015). Chitosan and its modification are broadly used as a non-viral vector of introduction of biomacromolecules and low-molecular medical preparations in gene therapy of cancer and potential immune adjuvant for anti-tumour vaccines (Babu & Ramesh, 2017; Ye et al., 2019). Moreover, combination of analytical and genome approaches allowed prediction and synthesis of hypothetical analogues from a limited bioresource of natural products, which have new properties, differing from the initial (Smith et al., 2018). Cancer tumours are accompanied by chronic inflammation and synthesize a number of signal molecules, preparing grounds for their own development and formation of metastatic niches that increasingly colonize a large space. Therefore, some of the most promising directions in cancer therapy would be the methods oriented at cancer signal molecules, effector cells, system of mediators of chronic inflammation, micro-environment of tumours, metastatic niches. The effectiveness and tolerability of some anti-tumour preparations are known to depend on the geno-

type of the patient, and therefore in the future, anti-tumour therapy will be of personalized pattern with consideration of the genotype peculiarities of the person.

Nanotechnologies are actively used in ongoing work on developing multi-modal systems to diagnose tumour diseases and transport preparations using hybrid particles based on biocompatible polymers that contain magnetic nanoparticles, photoacoustic, fluorescent and medical components (Novoselova et al., 2021). To transport drugs to tumours, biodegradable nanopolymer particles of marine origin are actively being used: chitosan, carrageenan, alginate, fucoidan (Gagliardi et al., 2021). Chitosan is a universal cation polysaccharide of marine origin, which was approved by the FDA as a nano-carrier of medical preparations. It is used in nanomedicine due to its unique cation properties, non-immunogenicity, biodegradation and biocompatibility (Islam et al., 2017; Al-Musawi et al., 2020; Islam et al., 2020). Carrageenan is a sulfated polysaccharide from brown algae, has a low potential to produce nanoparticles, but at the same time leads to prolonged release of medical agent from the epithelial and mucous tissues (George et al., 2019). Alginate is a linear anion polymer obtained from brown algae, is well soluble in physiologic fluids, interacts with various bioactive substances as a nanocarrier. Alginate nanoparticles are obtained using different methods, allowing one to combine them with various materials, for example nanoparticles based on chitosan, chemo-preparations doxorubicin, 5-fluorouracil (Boekhoven et al., 2015), use in technologies with addition of superparamagnetic particles of iron oxide (Ma et al., 2008; Wang et al., 2017), in tissue engineering (Singh et al., 2020). Fucoidan is a sulfated biopolysaccharide from brown marine algae, which has a broad range of biological, including anti-tumour, activities (Fitton et al., 2019), plays a great role in development of nano- and micro-particles, is used as a nanocarrier and drug agent (Hsu et al., 2019; Wang et al., 2019). As nanocarriers of drugs, ulvan and laminarin, obtained from brown algae are also being studied. All mentioned polysaccharides are studied in the field of nanomedicine not only as a system of transport of drugs to tumours, but also as drugs because of the many effects they exert: induction of apoptosis, regulation of signal transduction pathways, inhibition of migration and angiogenesis, modulation of immunity and antioxidant system (Zhong et al., 2020). Aside from targeted impact on tumour tissues, natural nanoparticles with chemotherapeutic load are able to overcome natural biological barriers, thereby coming to the organism's hardest places to reach (Tan et al., 2020). The greatest advantages of natural nanocarriers are non-toxicity, biocompatibility and biodegradability, which make them more promising for development of new methods of combating oncological diseases. Thus, natural compounds from marine organisms are studied and used as monopreparations, nanocarriers, chemotherapy loads, molecular vectors for transport of cytotoxic loads to the tumour tissues (Tursunova et al., 2018; Ou et al., 2020; Subjakova et al., 2021).

Conclusions

Medical resistance, genetic mutation, and population growth contribute to the emergence of new pathogens that cause diseases which were unknown earlier. This dictates the necessity of development of new drugs and improvement of the existing ones. The review presents the most recent data on contemporary biologically active compounds of marine origin, their value in practical medicine, biomedical and pharmaceutical spheres. Annually, 1,000 new molecules are being isolated from marine organisms, many of which have complex molecular structure, contain many potentially bioactive groups with so far undetermined mechanism of action (Van Andel et al., 2018). Marine organisms are used not only to obtain biologically active combinations, but in some cases as experimental models with unique experimental properties that provide additional possibilities for modeling and studying the biology of cancer (Elliot et al., 2020). Active interaction between representatives of various directions of science, medicine and industry would allow an effective implementation of all the stages of obtaining the final pharmaceutical product from marine organisms starting from the moment of discovery to use in practice – identification of combinations, determining their biological activity, chemical synthesis, development of methods of targeted transport, clinical trials, to introduction into production (Newman, 2016; Barreca et al., 2020).

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