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

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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 adhesia, mesenchimal 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 monopreparations 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 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 pharmacutical industries.

Keywords: cancer; marine organisms; preparations; cytotoxic preparations; clinical studies.
organisms. In the period from 1994 to 2014, from ascidians, there were coastal and deepwater zones. Ascidians produce a large amount of toxic, anti-diabetes, anti-proliferative, anti-parasitic activities (Palanisamy effectively treat various types of tumours (Calcabrini et al., 2017). In this affect several etiopathogenic links of carcinogenesis at the same time and newly 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 (Dishiovlo & Honeyek 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 Ascidiaeae, 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

Ascidiaeae. There are known single and colonial forms that live in coastal and deepwater zones. Ascidians produce a large amount of toxic secondary metabolites that protect them against predators and biofouling organisms. In the period from 1994 to 2014, from ascidians, there were isolated 580 compounds with antibacterial, anti-inflammatory, anti-virus, 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, Polycteniidae and Polyclitidae families, and out of 69 representatives of Didemnum genus, there were isolated 212 biologically active compounds (Duaa et al., 2020). The high pharmacological potential of nonribosomal peptides, proline-rich cyclic peptides and many compounds of various chemical classes produced by ascidians, and clinical application of them for the treatment of broad range of diseases, including in oncology, are well known (Duaa et al., 2020). In experiments, toxic metabolites of ascidians exerted effects on DNA transcription, protein translation, processes of neurohumoral regulation, cytoskeleton (Agrawal et al., 2016; Fang et al., 2016; Negi et al., 2017; Anumugam, 2018). Practical medicine uses 4 drugs derived from ascidians to treat patients suffering oncological diseases: Trabectedin, Apilin®, Midostaurin, Lurbinectin.

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 spiral 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: averanos, aristatastear, halichondrin, malanam, spongastatin, dactylocliastrum, diocistatin, discodermolide, herniales, laulimalide, pelorusside A and zampanolide (Mehtab et al., 2014; Gnanamal & Lakshmi, 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 these 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: Fludara, Cytarabine, Neldarabine, 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, steroids, polyketides, canthinoids, terpenes, polypropionates, macrolides, polysaturated 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; Esmeesalidian et al., 2018; Avila & Angulo-Precxlor, 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, Polatuzumab 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, cognitiverestoring, 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 prominent 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 completely organized procariotic 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 polyketides, alkaloids, steroids, terpenes, polyphenols, antitumours, and other organic compounds. Thus, dolastatin 10, obtained from some species of cyanobacteria and the marine mollusk *Dolabella auriculata*, 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, immuno-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 phototropic 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 (Chen et al., 2015; Martínez Andrade et al., 2018). Biopolymers of marine algae are known for their broad range of pharmacological effects: cytostatic, anti-proliferative, antitumour, proapoptotic, antigeneic, and immuno-modulating, 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 (dopanol and dopalan), 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 (Abidizadehaghi 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 (Balasubramaniam 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 reproduction. 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 steroids, alkaloids, peroxides, terpenes, fatty acids, derivatives of amino acids, cyclic peptides, depsipeptides, polyketides, xanthones, toxins, brystainostes 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; Gavrilidou 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 biocative potential (Avila & Ángulo-Pérez, 2020).

To identify the most bioproductive communities and their pharmaco-logical 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 *Ascidiaea*, but recent studies have revealed that biologically efficient products are synthesized by *Ascidiaea* 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 antigenic 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 (“immune-conjugants”). In clinical practice, monoclonal antibodies demonstrated a large potential and efficiency as new classes of prepara-
rations. An antibody-drug conjugate (ADC) is a three-component mole-
cule that consists of antibody (unit of selective targeting), medical cytotoxic-
preparations (beneficial loads) and chemical/peptide linker that com-
bines 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
suspects 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 aurista-
tins (monomethyl auristatin A and monomethyl auristatin F), powerful
anti-tubulin agents, synthetic analogues of marine dolastatin 10, which are
cytotoxic ultrapotent inhibitors of microtubules (Johansson et al., 2017).
Monomethyl auristatin E (MMAs, 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 medi-
cal preparation, and is applied as beneficial medical load in the content of
ADC. Monomethyl auristatin F (MMAF) is a powerful inhibitor of tubu-
line polymerase. It is different from MMAE because the residue of nore-
phedrine is replaced by phenylalanine and because of the lower penetrabil-
ty to the cells. By overcoming internal resistance of the tumour, auristatin
increase sensitivity of cells to tonizing 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 immu-
ne- 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 overcom-
ming 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 out-
standing 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 sphe-
res of science, practical medicine and industry.

Currently, 12 preparations are in use obtained from marine organ-
isms, 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, Nalname, Eribulin mesylate, Brentuximab vedotin,
Trabectedin, Plitidepsin, Enfortumab vedotin, Polatuzumab vedotin,
Belantamab mafodotin, Lurbinectinib), 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

| Name of drug/ Company | Marine organism / chemical class | Purpose, target | Mechanism of action | Reference |
|-----------------------|----------------------------------|----------------|---------------------|-----------|
| Fludarabine (Fidara: F-ara-AMP, AdPnP-F-araAMP/ PNP)/ Therapeutics, Inc. | Fungi / Nucleoside | Leukoses, lymphomas | Cytostatic of the group of purine antagonists, inhibitor of key DNA enzymes, apoptosis inducer | Lowe et al., 2018; Barrea et al., 2020; Cooper et al., 2020. |
| Cytarabine (ARA-C, Cytarabine): Pfizer | Fungi / Nucleoside | Leukoses | Inhibitor of DNA-polymerase, damages DNA in S-phase of cellular cycle | Salehi et al., 2019; Frankel et al., 2020. |
| Nalname (Ammonia): National University School of Medicine | Fungi / Nucleoside | Leukoses, lymphomas | Purine antimitobolite, accumulates mostly in T-cells, mechanism of action is similar to cytobarin | Barrea et al., 2020; Dunsmore et al., 2020. |
| Midostaurin (PKC-412): Novartis Pharmaceuticals, Stichting Hemato-Oncologie voor Volwassenen Nederland | Ascidiae, Actinobacteria / Indolocarbazole | Acute myelogenous leukemia, hematologic cancer | Multi-target inhibitor of protein kinase 3 (FLT 3), active against oncogenic CD 135 | Barrea et al., 2020; Orgaena et al., 2020; Morell et al., 2021. |
| Enfortumab vedotin (ET-743): 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; Tolyaney et al., 2020; Yuan et al., 2021. |
| Brentuximab vedotin (SUN 35, Oncode): Seattle Genetics | Mollusks, cyanobacteria / ADC with MAAE | T-cellular lymphomas, Hodgkin lymphoma | First target ADC-preparation. Targeted at CD30-positive tumour cells, microtubules | Chen et al., 2020; Strauss et al., 2020. |
| Trabectedin (ET-743): Yondelis): Phannacmar | Ascidiae / Alkaloid | Progressive liposarcoma, metastatic sarcomas of the soft tissues | Pleitropic mechanism of action, has effect on the key cellular processes and micro-environment of tumour | Mia et al., 2019; Kubayashi et al., 2020; Martinez-Tuirero et al., 2021. |
| Plitidepsin (dehydrodidemnin B, Apilimid): Pharmamar | Ascidiae / Cyclodepsipeptide | Metastatic breast, liver, and other solid cancers | Specifically binds with dFF12A, activates RAC1 and phosphorylation of JNK1, induces apoptosis depend-
ing 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 | Poppov, 2006; Xu et al., 2012; Newman & Cragg, 2014; Alonso-Álvarez et al., 2017; Xing et al., 2017; Martinez Andrade et al., 2018; Pereira et al., 2019; Losada et al., 2020. |
| Enfortumab vedotin (AGS-22MSE): Agenys, Seattle Genetics, Astellas Pharma | Mollusks, cyanobacteria / ADC with MAAE | Multiple solid tumours, metastatic cancers of the urinary system and the mammary glands | The first and the only agent aimed at recticulin-4, active against all 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 diffuse 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; Nejadneghbadmar, 2019; Pereira et al., 2019; Araya et al., 2020; Choi & Diefenbach, 2020. |
| Belantamab mafodotin (GSK2537916, Blenrep™)/ Decoys | 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; Taogari et al., 2020; Musahani et al., 2021. |
| Lurbinectedin (LY-01017, PM-01183, Zapsyu, Zepzela™)/ PharmaMar | Ascidiaeae / Alkaloid | Sarcomas of the soft tissues, 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; Takashita et al., 2016; Beldjorne et al., 2017; Calvo et al., 2017; Martinez Andrade, 2018; Kaufmann-Guernro, 2020; Madkham, 2020. |
| Placinibulin (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; Martinez Andrade et al., 2018; Pereira, 2019; Jimenez, 2020; Tonra et al., 2020. |
| Marizomib (SalinospongiaeA. NPI 0052)/ Nereus Pharmaceutical, Celgene, Triphase | Actinomyctes / 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 tetnoxin, active site of 20S-proteasome | Martins et al., 2014; Jensen et al., 2015; Perez-Perez et al., 2016; Pereira et al., 2019; Roth et al., 2020; Strom & Li, 2020. |
| Deputuzumab mafodotin (dpptux-m, ABT-414, ABT 806)/ Abbvie | Mollusks, cyanobacteria / ADC with MMAE | Squamous cell cancer of the lungs, glioblastoma multiforme | Blocks EGFR epitope on the surface of cell, internalizes and releases cyto-mMAF (cyto-mafodotin), binds with the network of microtubules, suspending the proliferation of tumour cells | Pereira et al., 2019; Bitlge et al., 2020; Van Den Bent et al., 2020. |
| Oligo-fucoidin / 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. |
| Tositumab vedotin (Hu Max 5-TF-ADC, TF-011-MMAE)/ Genmab, Seattle Genetics | Mollusks / ADC with MMAE | Metastatic cervical cancer, endometrial cancer, bladder cancer, prostate cancer, esophagus cancer, squamous cell carcinoma of the head and neck | The first ADC in its class, which contains human tissue factor (TF)-specific monochonal antibody. Inhibitor of microtubules, immune-toxin | De Bono et al., 2019; Newman, 2019; Pereira et al., 2019; Hong, 2020. |
| AG8-163CF (AGS-163BF)/ 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 phosphodiestere 3, ectonucleotide pyrophosphatase (ENPP3) | Newman & Clegg, 2017; Goggin & Hannam, 2018; Pereira et al., 2019; Kollmannsberger et al., 2021. |
| Telotuzumab vedotin (ABBV-3999)/ AbbVie | Mollusks, cyanobacteria / ADC with MMAE | Recurring and stage IV of lung cancer, advanced cancers of cancer | The first ADC in its class that contains humanized monoclonal antibody ADT 700. Aimed at α-Met expressing tumour cells | Stucklerie 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; Martinez Andrade et al., 2018; Yang et al., 2019; Ratrayake et al., 2020. |
| KRN ’7000 (Agelaspin derivative)/ Shanghai Public Health Clinical Center | Fungi / α-Galactosylceramide | Cancers of the lungs, stomach, kidneys, liver | Inducer of stable proliferation and production of interleukins of INK7 cells | Fuji et al., 2000; Anderson et al., 2013; Hartmann et al., 2020; Wisshah et al., 2020. |
| Ceprtuzumab vedotin (UC661/ADC3)/ UC San Diego | Various / ADC with MMAE | Solid tumours, B-cell lymphocytic leukemia, mammary cancer | Targets epitope of ROR1. Competitive inhibitor of binding ligand WNT, interrupts signal cascade associated with effects of ROR1 | Choi et al., 2015; Choi et al., 2018; Menek et al., 2021. |
| XMT 1536 (Upilatuzumab nilsofodotin)/ Mensana Therapeutics, IQVIA Biotech | Mollusks, cyanobacteria / ADC Dolaflexin with MMAF | Platinum-resistant ovarian cancer, metastatic non-small-cell lung cancer, tumours that express NaP/2 | Novel technology of ADC, contains α-Met-associated with effects of ROR1 and induces apoptosis and phosphorylation of Bcl-2 in some types of malignant cells. Suspends cellular cycle in phase G2-M | Maroszyno & Oxalito, 2020; Yurkovetsky et al., 2021. |
| MORAb-202 / Eisai Inc. | Fungi / ADC (contains farletuzumab and eribulin) | Solid tumours | Humanized antibody farletuzumab against folic receptor FRa, beneficial load – eribulin MTA (derivative of halichondrin B). Inhibitor of microtubules | Cheng et al., 2018; Matsunaga et al., 2021. |
| Soboludotin (Tzf-1027, derive 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; Fraa et al., 2019. |
| Placebulin (PM 009184, 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. |

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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)/ Intral, Rockville, 
Immacucell®, Bioyn 
Azarnémittl-GmbH, 
Fellbach, Calbiochem | Mollusks / Glycoprotein | Metastatic cancer of mammary gland, bladder cancer, ovary cancer, cancers of the pancreas, prostate, recurring glioblastoma, 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 | Newman & Cragg, 2012; 
Wimmers et al., 2017; 
Newman, 2019; 
Román, 2019. | III |
| Badarazarnab vedotin 
(DC509760A, 
R07032005) / Hoffmann-La Roche | Various / ADC with MMAE | Recurring or refractory B-cell lymphoma | Targets CD-70-A cells | Liersch et al., 2005; 
Sahlmann et al., 2017. | II |
| Indoxanab Vedotin 
(ML-0264, 
5F9vcMMAE, 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, 2019. | III |
| Patinazanab vedotin 
(DCDT2980S, 
FCU72803) / Genentech, Roche | Mollusks, cyanobacteria / ADC with MMAE | Non-Hodgkin lymphoma, leukemia | Stimulates processes of apoptosis, inhibits processes of myosin, polymerisation of tubulin, targets CD22 | Forero-Ferrés et al., 2016; 
Advani et al., 2017; 
Morschhauser et al., 2019; 
Yu et al., 2021. | III |

Regul. Mech. Biosyst., 2021, 12(2)
| Name of drug / Company | Marine organism / chemical class | Purpose, target | Mechanism of action | References | Phase of study |
|------------------------|----------------------------------|-----------------|---------------------|------------|---------------|
| Glutathionin (CDX-011, CR0111) / Seattle Genetics, Celldex Therapeutics | Mollusks, cyanobacteria / ADC with MMAGE | Squamous cell lung cancer, melanoma, triple negative breast cancer of the mammary gland, recurring osteosarcoma, uveal melanoma | Induces partial or complete regression of cancer cells that express GPNNMB, inhibits the set of microtubules | Ott et al., 2019; Patrick et al., 2019; Pereira et al., 2019; Wolda-Wahser & Robak, 2019; Hassanov et al., 2020; Kasilan et al., 2020. | III |
| Tasidotin (ILX-651, derivate Dolastatin 15) / Genentech | Mollusks / Pentapeptide | Erythroid leukosis, ovary cancer, carcinoma of the large intestine, cells of mammary cancer, lung carcinoma, melanoma | Initiates processes of proliferation, myosis, polymerization of tubulin in microtubules | Ray et al., 2007; Martini et al., 2014; Frau et al., 2019. | III |
| PF-06263597 (Alimetrex) / Pfizer | Mollusks, cyanobacteria / ADC with MMAGE | Progressive solid tumours, leukoses | Fragment of antibody selectively binds with FTY7expressing cells. Inhibits polymerization of tubulin, leads to suspension of phase G2 / M and apoptosis of tumour cells | Forese-Fortes et al., 2016; Shapiro et al., 2017; Gogineni & Hannam 2018; Newman, 2019. | I |
| DMUC-5754A (Solitauhimab vedotin, RG-7458) / Hoffmann-La Roche Ltd, Genentech | Mollusks, cyanobacteria / ADC with MMAGE | Ovary and pancreatic cancers | Contains humanized monoclonal antibody against MUC16. Inhibitor of tubulin polymerase, apoptosis stimulator | Newman & Crigg, 2014; Liu et al., 2016; Gogineni & Hannam, 2018. | I |
| Eliquispan (PMD2734, Invalse, 15b) / Pharma Mar | Mollusks / Depsipetide | 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 |
| Breyzosyne-1 / National Cancer Institute (USA) | Bryozoa / Macrocyst | Melanoma, lymphoma, ovary carcinoma, liver carcinoma, leukosis. Orphan drug in combination with paclitaxil as esophagus cancer treatment | Selective inhibitor of non-type isoform of protein kinase C. Induces synthesis of cytoterix, immune-stimulator | Popov, 2006; Kim & Ganesan, 2015; Ciavatta et al., 2020; Raghavan et al., 2020. | I |
| DNB-060A (Lifastuzumab vedotin, RG-7599, GTPI8405) / Genentech Inc. | Mollusks, cyanobacteria / ADC with MMAGE | Non-small-cell lung cancer, platinum-resistant ovarian cancer | Targets NaP2b epitope, blocks polymerization of tubulin | Newman & Crigg, 2014; Gerber et al., 2020; Moore et al., 2020. | I |
| DMOT-4099A (RG-7600) / Genentech Inc. | Mollusks, cyanobacteria / ADC with MMAGE | Inoperable pancreatic or platinum-resistant ovarian cancer | Contains humanized IgG1-anti-mesothelin in MAb h7D9 v3. Destroys the microtubule network, induces apoptosis | Newman & Crigg, 2014; Weekes et al., 2016; Gogineni & Hannam, 2018. | I |
| DEN-5252A (RG-7636) / Genentech, Seattle Genetics | Mollusks, cyanobacteria / ADC with MMAGE | Inoperable melanoma | Anti-microtubule agent, inhibitor of tubulin-polymerase, matosis, apoptosis inducer | Newman & Crigg, 2014; Gogineni & Hannam, 2018; Nejadomhardakdans et al., 2019. | I |
| Vandotuzumab polidotin (PFO-46647020) / Pfizer | Mollusks, cyanobacteria / ADC with MMAGE | Metastatic prostate cancer | Modified humanized antibody against STEAP1. IgG1, bond with MMAGE through Mc-V-C-PARC. Aims at epithelial prostate antigen | Newman & Crigg, 2014; Van Andel et al., 2018. | I |
| Sirtuduzumab vedotin (AGS-15E, AGS-15ME) / Agensys, Seattle Genetics | Mollusks, cyanobacteria / ADC with MMAGE | Cancers of the bladder, lungs, mammary gland, glioblastoma | The first and the only agent aimed at transmembrane protein SLITRK6. Effectively binds with target cells, induces apoptosis | Holland et al., 2016; Pytlik et al., 2016; Pereira et al., 2019. | I |
| AGS 67E / Agensys Inc., Astellas Pharma | Mollusks, cyanobacteria / ADC with MMAGE | 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 |
| Coletuzumab polidotin (PF-06647020) / Pfizer | Mollusks / ADC with auristatin (anti-PTK7) | Solid tumours | Matosis inhibitor, apoptosis stimulator, inhibitor of tubulin-polymerisation | Kafish, 2017; Newman, 2019. | I |
| PF-06380101 (Q8020A/34E) / Pfizer | Mollusks, cyanobacteria / ADC with MMAGE | 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-0855 (Samrotomab vedotin) / AbbVie Inc. | Various / Anti-hu-RCC15 ADC | Solid tumours, undifferentiated pleomorphic sarcoma, squamous cell cancer of the head and neck, mammary gland cancer | Aims at LRRC15 in the macro-environment of tumour | Madonna et al., 2014; Parcell et al., 2018; Pereira et al., 2019; Hingorani et al., 2021. | I |
| XMT 1522 (ITAK-322) / Merzalana Therapeutics | Various ADC with MMAGE-HPa | Solid tumours, lung, gastric glands | Anti-Hae2-antibody-medical preparation | Hamilton et al., 2018; Le Joncour et al., 2019. | I |
| NeuromastinE: 5974 / 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 (3e9MMAGE) / Seattle Genetics | Mollusks, cyanobacteria / ADC with MMAGE | Progressing solid tumours, CAV9-positive stomach cancer | Targets carbonic anhydrase IX (CA-9) of human, inhibitor of tubulin polymerization | Francisco et al., 2003; Petral et al., 2012. | I |
| Demirizuminab mafidotin (SGN-CD19A, SGN-19A: BU21-401) / Seattle Genetics | Mollusks, cyanobacteria / ADC with MMAGE | CD19-positive acute lymphoblastic leukaemia, 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 Nemery & Teachey, 2021. | I |
| SGN-75 (Vincze- tuhimab mafidotin) / Seattle Genetics | Mollusks, cyanobacteria / ADC with MMAGE | Recurring and refractory non-Hodgkin lymphoma, hepatocellular adenocarcinoma | Induces apoptosis of tumour cells, inhibits proliferation of tumour cells that overexpress CD70 | Tummar et al., 2014; Pereira et al., 2019. | I |
Trials of biopharmaceutic 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 – 1,100 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 chemothapeutic 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 turnour diseases is played by infectious agents (Pirinen 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, anti-viral, immune-modulating, neuro-protective, antibacterial and many other effects, can make a systemic multi-target impact on cancer cells, as well as infectious agents (Fittou et al., 2020; Gentile et al., 2021; Tagliatela-Scafati, 2021). Accordingly, a drug of marine origin Plitidipsin (Aplidin™), used to treat tumour diseases, in its 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 Plitidipsin, such preparations as Erbulin 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 (Kallotta 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, SIV, KIV, HAV, HCV, EBV, enterovirus, HCMV, JEV, TMV, PTV, 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 (Ricco 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 preclinical 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 tunicata), 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 (Calabretta 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, talbotulin, ceramide, cryptoficine, discodermolide (Porziani 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 chemotherapy 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, sRNA and DNA-lyngands 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 chemotherapeutic inhibition 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 sustain stem cells, including autologous 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 siGI2LO-LODE™ (resinatature biodegradable implant based on small interfering RNA, which is aimed specifically at KRAS oncogene) to treat locally advanced pancreatic cancer (Gulan 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 hypothetic analogues from a limited biorepository 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, phototoxic, fluorescent and medical components (Novoselova et al., 2021). To transport drugs to tumours, biodegradable nanoparticles 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-immunogenity, biodegradability 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 (Filton 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 antiangiogenic 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, chemotherapeutic preparations, molecular vectors for transport of cytotoxic loads to the tumour tissues (Tursanuva 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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