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PRACTICALLY VALUABLE METABOLITES OF MARINE MICROORGANISMS

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The review considers the modern literature data on the synthesis by fungi, actinobacteria, and bacteria isolated from marine ecosystems (seawater, bottom sediments, flora and fauna, mangrove biomes, glaciers), practically valuable metabolites. Marine microorganisms synthesize a wide range of practically valuable enzymes (cold-active galactosidase, agarase, alginate lyase, fucoidase, chitinase, etc.), surface-active glyco- and lipopeptides with emulsifying, antimicrobial and antiadhesive activity, as well as secondary metabolites with diverse biological activity (antimicrobial, antitumor, cytotoxic). However, the use of marine producers in biotechnological processes is constrained by their low synthesizing capacity and high costs of biosynthesis (complex nutrient media and expensive carbohydrate substrates). In biotechnology, marine microorganisms can be used as sources of genes encoding the synthesis of new biologically active substances with unique properties, including antimicrobial and antitumor.

Key words: marine fungi, bacteria, biologically active substances.

The unexplored marine world, which is characterized by great biodiversity, is a resource for discovering new structures with unique properties. The prolonged evolution of marine life has led to the emergence of species with atypical genes. Marine microorganisms had to adapt to such living conditions as high pressure (up to 1100 atm), anaerobic conditions at great depths at temperatures slightly below 0 °C, high acidity (pH 2.8), and temperatures (above 100 °C) in the area of thermal springs. Also, it was necessary to adapt to high salinity, radiation, light, low concentrations of nutrients [1]. Existence in such conditions, close to the extreme, contributed to the genetic and metabolic diversity of marine microorganisms, which in turn led to the emergence of specific adaptation mechanisms, in particular, the synthesis of unusual protective compounds. It is now found that marine microorganisms can synthesize a huge number of unique metabolites with various biological properties, which are promising for use in the pharmaceutical and cosmetic industries, medicine [2–5]. For example, the hydrolytic enzymes of these microorganisms can function under conditions that lead to deposition or denaturation of most proteins synthesized by mesophilic (terrestrial) microorganisms [6]. Besides, seawater, which is physiologically and chemically close to human blood plasma, can provide the synthesis of biomolecules, which are characterized by lower toxicity and having fewer side effects when used for therapeutic purposes compared to enzymes produced by traditional producers [6].

Therefore, it is not surprising that every year the number of publications devoted to the study of marine microorganisms as producers of various biologically active compounds

increases [7–18]. In the last 5 years, about 400 reviews have been published with the keyword "marine microorganisms". However, such reviews are "narrowly specialized" because they summarize publications related to the formation of antibiotics by marine microorganisms [10, 15], antitumor compounds [13], enzymes [16], polysaccharides [11], or those, which consider the ability of sea fungi [4, 5, 7], actinobacteria [1, 3, 9, 14], algae [17] to the synthesis of certain metabolites. Also, much attention in the most such reviews are paid to the biodiversity of marine microorganisms [1–3, 7], determination of the chemical composition and structure of metabolites [4, 7, 9–12, 14, 15, 17, 18], their biological activity [8–10, 13–17]. Yet the prospects of marine microorganisms using in biotechnology are not considered.

The purpose of this review was to analyze and summarize current literature data on the biotechnological potential of marine fungi and bacteria as producers of a wide range of practically valuable products (surfactant glyco- and lipopeptides, exopolysaccharides, enzymes, metabolites with various biological activity — antimicrobial, antitumor, cytotoxic).

Surfactants

Due to the advantages of microbial surfactants over synthetic analogs (biodegradability, non-toxicity, stability of physicochemical properties in a wide range of temperature and pH), as well as their unique biological properties, interest in these substances is growing every year [19–21]. So, the possibility of using microbial origin surfactants in the oil and mining, chemical, food industries, agriculture, in environmental technologies for environmental cleansing has been already found.

In recent years, a significant number of papers had been published in which it was reported about the isolation of marine microorganisms capable to synthesize surfactants [22–50]. Among marine bacteria, the representatives of *Bacillus, Pseudomonas, Rhodococcus* genera were found [32, 34, 35, 41–43, 45, 46, 49], which were the known producers of surfactants [33]. However, many isolated strains turned out to be the non-traditional producers of surfactants — members of the genera *Buttiauxella* [22], *Serratia* [23], *Staphylococcus* [24, 25], *Vibrio* [28], *Haloimonas* [30], *Nesterenkonia* [37], *Achromobacter* [40].

Analysis of the literature data on the physicochemical and biological properties of surfactants synthesized by marine microorganisms showed that they were virtually indistinguishable from those established for surfactants formed by traditional producers. Thus, by chemical nature, most surfactants of marine microorganisms were glycolipids [22–32] or lipopeptides [34–43]. They were characterized by antimicrobial [22–26, 37–39], antiadhesive [23, 24] and antioxidant [37] activity, as well as the ability to destroy biofilms of pathogenic microorganisms [22–25, 38], emulsification and solubilization of various hydrocarbons [26–30, 32, 34–36, 41, 44].

Notably, that in [22–29, 34–41, 44] the ability to synthesize surfactants was evaluated mainly by the indicators of emulsification index, surface tension, critical concentration of micelle formation, which indicated only the presence of surfactants, not their amount. Therefore, to assess the level of synthesizing ability of marine microorganisms and compare with that of traditional surfactant producers was not possible. Also, in these works, the authors focused on the properties of surfactants to predict the prospects of their practical significance.

Glycolipids of marine microorganisms

It was found that the marine halotolerant strain of enterobacteria *Buttiauxella* sp. M44 synthesized a glycolipid consisting of glucopyranose, associated with fatty acids C14, C16, and C18, including octadecanoic acid [22]. Glycolipid was characterized by antimicrobial activity against some pathogens (*Escherichia coli* ATCC25922, *Bacillus subtilis* ATCC465, *Bacillus cereus* ATCC11778, *Candida albicans* ATCC10231, *Aspergillus niger* (strain number was not given), *Salmonella enterica* in concentrations of 100–300 μg/ml.

Dusane et al. [23] reported a glycolipid synthesized by another member of the marine enterobacteria *Serratia marcescens* CFS, which had antimicrobial and antiadhesive activity. Glycolipid contained glucose and palmitic acid. The minimum inhibitory concentration (MIC) of this surfactant against *C. albicans* BH and *Pseudomonas aeruginosa* PAO1 were 25 μg/ml, against *Bacillus pumilus* TiO1 — 12.5 μg/ml. Glycolipid of the CFS strain at a concentration of 50–100 μg/ml reduced the adhesion of these test cultures to polystyrene by 75–94% and destroyed their biofilm by 55–80%.

The report [24] concerning the surfactant synthesis increase in case of co-cultivation

of the producer *Staphylococcus lentus* SZ2 isolated from a sea snail surface with *Vibrio harveyi* aquaculture pathogen is rather interesting. At the end of co-cultivation of both strains, the growth of *V. harveyi* was completely inhibited, and the surfactant formed under such conditions (called BS-SLSZ2) was characterized by the highest antiadhesive activity and ability to destroy biofilms compared to the drug formed by *S. lentus* SZ2 monoculture. By chemical nature, BS-SLSZ2 was a glycolipid preparation. It contained triose (a four-carbon carbohydrate) as well as hexadecanoic and octadecanoic acids. The glycolipid BS-SLSZ2 at a concentration of 20 μg/ml destroyed the biofilms of *V. harveyi* and *P. aeruginosa* by 78.7 and 81.7%, respectively. The disadvantage of strain SZ2 as a surfactant producer was low concentration of the target product, which even in case of co-cultivation with *V. harveyi* did not exceed 70 mg/l [24].

Another *Staphylococcus* genus, which synthesized glycolipid with similar biological properties, was a strain of *Staphylococcus saprophyticus* SBPS-15 isolated from oil-contaminated coastal waters [25]. The surfactant strain SBPS-15, which contained mannose and oleic acid, was named staphylosan. At concentrations of staphylosan 200–400 μg/ml, complete destruction of biofilms of *P. aeruginosa* BHKH-19 and *Serratia liquefaciens* BHKH-23 was observed. Destruction of biofilms of *Acinetobacter beijerinckii* BHKH-11, *Micrococcus luteus* BHKH-39, *B. subtilis* BHKH-7 and *Marinobacter lipolyticus* BHKH-31 by 93, 91, 90 and 85%, respectively, was achieved at a surfactant concentration of 400 μg/ml.

In addition to antimicrobial activity, glycolipids of marine microorganisms have emulsifying properties, due to which they can be promising for the degradation of oil pollution and polycyclic aromatic hydrocarbons [27–32].

It was found that *Dietzia maris* As-13-3 strain isolated from deep-sea thermal waters had synthesized dirhamnolipids during cultivation on hydrocarbons, olive oil, glycerol, and glucose [27]. Under conditions of strain As-13-3 growth on tetradecane, hexadecane, and pier, the surface tension decreased to 33–35 mN/m. Rhamnolipids formed stable emulsions with toluene, hexane, cyclohexane, hexadecane, pier, and diesel, so the emulsification index was 54–64%. The authors of [27] noted that the advantage of *D. maris* As-13-3 as a producer of rhamnolipids for environmental bioremediation was the non-pathogenicity of the strain.

Halomonas sp. MV-30, isolated from a sea sponge, synthesized glycolipids under conditions of growth on both glucose and hydrocarbons (reduction of surface tension to 30 mN/m) [30]. The emulsification index of glycolipids using crude oil as a substrate was 93.1%, kerosene — 86.6%. The emulsions remained stable for a month and were formed at temperatures above 80 °C, pH ≥ 7.0, and NaCl concentrations up to 10%. In the presence of partially purified *Halomonas* sp. MV-30 surfactant, degree of oil washing from sand was 62%. The authors of [30] noted that the glycolipids of strain MV-30 were promising for increasing oil production and bioremediation of hydrocarbons in extreme conditions.

It has been reported in [29] about isolation from sea water of *Nocardiopsis* sp. VITSISB strain, which synthesized rhamnolipids on an oil-containing medium. On a model system that simulated the spillage of engine oil in an ocean, the researchers found the possibility to use the cells immobilized in Ca^{2+} -alginate balls of the VITSISB strain for bioremediation of this xenobiotic. However, engine oil destruction occurred in the presence of sugar cane juice and soybean meal in an aquatic environment as sources of carbon and nitrogen, respectively. Rhamnolipids of *Nocardiopsis* sp. VITSISB strain proved to be stable in the temperature range 5–100 °C, pH 2–12, and sodium chloride concentrations 3–10%. The authors of [29] considered rhamnolipid-producing strain VITSISB as promising for the elimination of oil spills in the ocean.

Summarized information concerning glycolipids synthesized by marine microorganisms is given in Table 1. These data indicate that marine microorganisms synthesize glycolipids on various substrates, though mainly on fairly high-value (carbohydrates, hexadecane, purified glycerol). Lack of transparency on the synthesis of the target product enables to assess the prospects to use the strains as potential producers of surfactants. However, the stability of surfactants and their emulsions in a wide range of temperature, pH, and salinity make them attractive for practical application in environmental technologies for bioremediation of the environment.

Lipopeptides of marine microorganisms

Lipopeptides consist of a lipid moiety coupled to a short linear or cyclic oligopeptide [33]. The data presented in [34–41] show

that most lipopeptide surfactants of marine microorganisms are considered promising for use in bioremediation and environmental problems. It is known that the synthesis of lipopeptides by traditional producers (representatives of the genera *Bacillus* and *Pseudomonas*) is carried out mainly using carbohydrate substrates [33]. Similarly, marine microorganisms can synthesize lipopeptides under conditions of growth on carbohydrates [38, 39, 42]. However, many of them can metabolize agro-industrial waste and waste from other industries [34, 36, 37].

Mani et al. [34] isolated from marine sediments a *Bacillus simplex* SBN19 strain, which synthesized surfactants of lipopeptide nature in various waste oils.

Maximum concentration of surfactants (908 mg/l) was achieved under conditions of the strain SBN19 growth in fried sunflower oil. It was found that in the presence of purified lipopeptide (100 mg/l) after 24 h, the degree of washing of oil from contaminated sand (5 ml of oil per 100 g of sand) in the range of salinity 0–30% was 80–85% (with maximum salinity — 84.7%).

It was found [35] that *Bacillus stratosphericus* FLU5, isolated from oil-contaminated seawater, synthesized surfactants on a wide range of carbon substrates (crude oil, diesel fuel, engine oil, spent engine oil, corn and olive oil, refried oil, glycerol). Surfactant synthesis rates were the highest (1.88–2.25 g/l) in a process of growing the strain on oil-containing substrates. By chemical nature, *B. stratosphericus* FLU5 lipopeptides are a complex of surfactin and pumilacidin. The lipopeptide complex showed stability in a wide range of pH (2–12), temperature (4–121 °C), and NaCl concentration (0–25%). In the presence of supernatant after culturing the FLU5 strain on fried oil, the remobilization of motor oil hydrocarbons (20%) from contaminated soil was several times higher compared to the use of synthetic surfactants (Tween 20, Tween 80, Triton X-100 and SDS).

Vilela et al. [36] isolated from marine invertebrates the *Brevibacterium luteolum* AC189a strain, which synthesized surfactants of lipopeptide nature under conditions of mineral oil growth. The emulsification index of surfactants with different hydrocarbons was 60–79%. The lipopeptide showed the ability to clean sand from oil. In the presence of 0.1% surfactant, the degree of washing of oil (10%) from contaminated sand after 6 h was 83%.

It was reported [37] that the strain *Nesterenkonia* sp. isolated from the *Fasciospongia cavernosa* MSA31 sea sponge, which synthesized a lipopeptide when grown in olive oil, was characterized not only by emulsifying but antioxidant and antimicrobial activity as well. Thus, the level of neutralization of 2,2-diphenyl-1-picrylhydrazyl radical (DFPG) at a surfactant concentration of 6 mg/ml was 65%. At a surfactant concentration of 125 μg/ml, the destruction of *Staphylococcus aureus* biofilm was noticeable. Also, the authors used a lipopeptide of strain MSA31 as an emulsifier in production of muffins with a protective effect against *S. aureus*. The addition of lipopeptide to the dough at a concentration of 0.5–1% improved the organoleptic characteristics of the finished product [37].

Cyclic lipopeptide surfactant pseudofactin II, synthesized by the arctic strain *Pseudomonas fluorescens* BD5 [42] can activate the apoptosis of melanoma A375 cells as a result of the effect of surfactant micelles on the permeability of the cell membrane, accompanied by the release of lactate dehydrogenase and Ca^{2+} [38]. This lipopeptide reduced the adhesion of pathogenic microorganisms *Escherichia coli*, *Enterococcus faecalis, Enterococcus hirae, Staphylococcus epidermidis, Proteus mirabilis* and *Candida albicans* on glass, polystyrene and silicone, as well as prevented the formation of biofilms on medical materials. Pre-treatment of polystyrene with a solution of pseudofactin II at a concentration of 0.5 mg/ml reduced the adhesion of bacterial test cultures by 36–90%, and *C. albicans* — by 92–99%. Thus, pseudofactin II could be used as an agent against microbial colonization of various surfaces, such as implants or urethral catheters [43].

The *Aneurinibacillus aneurinilyticus* SBP-11 strain [39] under the conditions of growth on glucose synthesized lipopeptide surfactant aneurinifactin with high antimicrobial activity against pathogenic bacteria. Thus, the minimum inhibitory concentrations of aneurinifactin were (μg/ml) as follows: *Klebsiella pneumoniae* — 4, *E. coli* — 8, *S. aureus* — 8, *P. aeruginosa* — 16, *B. subtilis* — 16, *Vibrio cholerae* — 16. Also, at a concentration of 200 mg/l aneurinifactin, the degree of washing of oil from contaminated sand (5 ml of oil per 100 g of sand) after 24 h was 81% [39].

In [41], the authors investigated the possibility of intensifying lipopeptide

Table 1. **Synthesis of glycolipids by marine microorganisms**

Producer	Source of selection	Cultivation temperature	Source of carbon, g/l	Physico-chemical properties		Prospects for practical use	Literature
				chemical composition	stability		
Vibrio sp. 3B-2	Marine bottom sediments	28 °C	Lactose, 5	–	–	Bioremediation, increase of oil production	[28]
Buttiauxella sp. M44	Coastal waters	33 °C	Molasses, 10	glucopyranose, octadecanoic acid	20–60 °C, pH 7–8, salinity to 3%	Antimicrobial activity	[22]
Dietzia maris As-13-3	Deep-water hydrothermal vents	28 °C	Hexadecane, 20	dirhamnolipid	–	Emulsifier, bioremediation, hydrocarbon degradation	[27]
Staphylococcus lentus SZ2	The surface of the sea snail	30 °C	Casein hydrolysate, 10	triose, hexadecanoic, octadecanoic acids	–	Destruction of biofilms, antimicrobial and antiadhesive activity	[24]
Serratia marcescens CFS	Sea coral *Symphyllia* sp.	30 °C	Peptone, 5	glucose, palmitic acid	–	Destruction of biofilms, antimicrobial and antiadhesive activity	[23]
Staphylococcus saprophyticus SBPS-15	Oil-contaminated coastal areas	37 °C	Glucose, 20	mannose, oleic acid	4–80 °C, pH 3–9	Destruction of biofilms, antimicrobial and antiadhesive activity	[25]
Nocardiopsis sp.VITSISB	Seawater	37 °C	Oil, 0,5% (volume fraction)	rhamnolipid	5–100 °C, pH 2–12, salinity to 3–10%	Bioremediation, decomposition of oil and engine oil	[29]
Halomonas sp. MB-30	Sea sponge	30 °C	Oil, 2% (volume fraction)	–	5–100 °C, pH 2–12, salinity to 3–10%	Bioremediation, increase oil production	[30]
Streptomyces sp. MAB36	Marine bottom sediments	–	Starch, 15,8 Oil, 16 ml/l	glycolipid	30–50 °C, pH 5–9, salinity 1,5%	Bioremediation, antimicrobial activity	[26]
Rhodococcus sp. PML026	Seawater	30 °C	Sunflower oil, 2 % (volume fraction)	trehalose lipid	20–100 °C, pH 2–10, salinity to 25%	Bioremediation	[32]
Aureobasidium pullulans YTP6-14	Seawater	30 °C	Glucose, 50 Glycerol, 2,5%	Lactone 5-hydroxy-2-decanoic acid	4–100 °C, pH 2–12 salinity to 12%	Emulsifier	[31]

Note: «–» — no data.

synthesis by a strain of *Bacillus licheniformis* NIOTAMKV06 isolated from a sea sponge. Under conditions of growth of strain NIOTAMKV06 on glucose, the surfactant concentration was 1.8 g/l. After optimizing the composition of the nutrient medium it increased to 3 g/l. The use of a mixture of 20 g/l of glucose and 2.5% of oil as a carbon source made it possible to increase the concentration of surfactants to 6 g/l. The authors obtained a recombinant strain of *E. coli*, which synthesized 11.78 g/l of lipopeptide [41]. Surfactant *B. licheniformis* NIOTAMKV06 emulsified crude oil, kerosene, and diesel. This work was the first to report a highly active marine lipopeptide-producing strain.

Deng et al. [40] isolated from oil-contaminated seawater a strain of *Achromobacter* sp. HZ01, which on a medium with glycerol synthesized a new cyclic lipopeptide at a concentration of 6 g/l. This surfactant formed emulsions with coconut, peanut, sesame, soybean, sunflower, olive, corn oil, kerosene, and diesel fuel, and the emulsions were characterized by high stability in the temperature range of 40–100 °C, pH 6–12, and salinity of 0–3%.

It was found [44] that the *Marinobacter* sp. M22.20 strain isolated from marine sediments under conditions of growth in the medium with 2% (volume fraction) of soybean oil synthesized phospholipopeptides (concentration was not specified) with high emulsifying activity. The emulsions were stable when stored for 30 months at a NaCl concentration of 300 g/l, temperature of 4 °C and after heat treatment 120 °C, 20 min).

Summarized data on lipopeptides synthesized by marine microorganisms are given in Table 2. Lipopeptides are characterized by the same physicochemical and biological properties as glycolipids (Table 1). However, a significant advantage of lipopeptides is the possibility to obtain them on cheap and available industrial waste in large quantities.

During 2018–2019, several papers were published [45–49] on the synthesis of surfactant glyco- and lipopeptides by marine microorganisms, in which the authors studied in detail the chemical composition and/or biological (mainly antimicrobial) activity of surfactants, but did not provide conditions of cultivation and synthesis of surfactants. The review [50] provided information on the chemical composition and prospects of practical use of surfactants of marine microorganisms in medicine, perfumery, cosmetics, food industry, bioremediation, and noted that marine microorganisms were not currently promising biological agents for biotechnological processes, as they needed improvement methods of genetic and/or metabolic engineering.

Enzymes

Enzymes synthesized by marine microorganisms are characterized by high activity in a wide range of pH, temperature, light, pressure, salt concentrations, and are resistant to organic solvents, metal ions, detergents [16].

Recently, the number of publications on the synthesis of β-galactosidases by microorganisms, which show high activity at low temperatures (so-called cold-active β-galactosidases), has increased in the literature [51–57]. This is due to the following reasons. Firstly, it is the possibility to use these enzymes in the production of lactose-free dairy products, as well as to create biosensors that control the lactose content in their production. It is known that biosensors based on immobilized β-galactosidase can be used to analyze lactose in milk [51]. Interest in the production of lactose-free dairy products (milk, including condensed milk, ice cream) is because today a third of the world's population suffers from lactose intolerance [52, 53]. Secondly, the hydrolysis of lactose by cold-active β-galactosidase reduces the hygroscopicity of milk, thereby preventing its crystallization in ice cream and condensed milk. Also, the use of such enzymes at low temperatures minimizes the risk of microbial contamination of finished products [53]. Thirdly, the use of β-galactosidase for the destruction of lactose in serum can reduce wastewater contamination of dairy plants [52]. Most currently used β-galactosidases in the food industry (Maxilact, Lactozym, and neutral yeast lactase (DYL)) are mesophilic and have an optimum temperature of approximately 35 to 50 °C and are characterized by low activity at 20 °C.

Also, cold-active β-galactosidases can be used to produce water-soluble oligosaccharides that are less sweet than mono- and disaccharides. The interest in oligosaccharides is because they are prebiotics that activate the development of bifidobacteria in the intestine [56].

The largest number of producers of cold-active β-galactosidases is found among marine microorganisms. For example, the marine arctic bacteria *Enterobacter ludwigii* KS92 synthesizes

Table 2. **Synthesis of lipopeptides by marine microorganisms**

Producer	Source of selection	Cultivation temperature	Carbon source, g/l	Physico-chemical properties	Prospects for use	Literature
Bacillus stratosphericus FLU5	Seawater contaminated with oil	37 °C	Fried oil (1%, volume fraction)	4–121 °C, pH 2–12, salinity (0–25%)	Bioremediation, destruction of motor oil	[35]
Aneurinibacillus aneurinilyticus SBP-11	Marine bottom sediments	37 °C	Glucose, 15	4–80 °C, pH 2–9	Antimicrobial activity, increase oil production	[39]
Bacillus simplex SBN19	Marine bottom sediments	37 °C	Spent sunflower oil (2%, volume fraction)	salinity to 30%	Bioremediation, increase oil production	[34]
Pseudomonas fluorescens BD5	Arctic strain	37 °C	Glucose, 20	–	Destruction of biofilms, antimicrobial, antiadhesive and antitumor activity	[38, 42, 43]
Brevibacterium luteolum AC189a	Marine invertebrates	30 °C	Marine invertebrates (2%, volume fraction)	4–100 °C, pH 2–12, salinity (0–12%)	Bioremediation, increase oil production	[36]
Bacillus licheniformis NIOT-AMKV06	Sea sponge	38 °C	Glucose, 20 Oil 2,5%	20–70 °C, pH 5–10	Emulsifier. Bioremediation, increase oil production	[41]
Achromobacter sp. HZ01	Seawater contaminated with oil	28 °C	Glycerol, 40	40–100 °C, pH 6–12, salinity (0–3%)	Bioremediation. Emulsifier	[40]
Nesterenkoia sp. MSA31	Sea sponge *Fasciospongia cavernosa*	28 °C	Olive oil, 10	4–121 °C, pH 6–9 salinity (0–10%)	Antioxidant and antimicrobial activity. Emulsifier for the food industry	[37]

Note: «–» — no data.

β-galactosidase [52], which is characterized by high activity at a temperature of 15–25 °C and a pH of 5–10. At the same time, enzymes formed by deep-sea marine bacteria *Thalassospira* sp. 3SC-21 and *Pseudoalteromonas* sp. KNOUC808 showed maximum activity in the range of lower temperatures (from 4 to 20 °C), but at different pH values [53, 54]. The optimum pH of β-Galactosidase strain 3SC-21 was 6.5, and strain KNOUC808 — 7–8. β-galactosidase synthesized by another deep-sea bacterium *Alteromonas* sp. ML52 [55], was also characterized by high activity at a temperature of 4–25 °C. Thus, marine microorganisms existing in the polar and other regions, where the average annual temperature does not exceed 5 °C, are a source of virtually valuable cold-active β-galactosidases.

Commercial α-amylases are inactivated at low pH and high temperatures, but these conditions must be maintained at the stage of starch saccharification during molasses production. In turn, α-amylase synthesized by the marine bacterium *Geobacillus* sp. 4j

was active in the pH range of 4.5–7.0 and at a temperature of 55–90 °C [58]. In this work, the authors investigated not only the properties of the enzyme but also optimized the conditions for culturing strain 4j in flasks and a bioreactor. This made it possible to increase significantly its activity. Thus, in the process of *Geobacillus* sp. 4j growing in flasks on an optimized medium with starch as a carbon source, the amylase activity was 6.4 U/ml, which is 5 times higher than before optimization. Cultivation of the producer in a 15 l bioreactor at a temperature of 60 °C, an initial pH value of 6.0 and maintaining the dissolved oxygen concentration at 20% of air saturation allowed to increase the activity of the enzyme to 79 U/ml [58].

Currently, proteases account for 60% of the world market for enzymes, and what is more, proteases that are highly active in a wide range of pH and temperature, in the presence of metal ions and organic solvents are in great demand [59]. These requirements are met by an alkaline protease synthesized by the *Staphylococcus saprophyticus* BUU1 strain, which is isolated from marine sediments. Protease was characterized by stability at temperatures from 10 to 80 °C, pH from 3 to 12, in the presence of dodecyl sulfate, hydrogen peroxide, bleaching agents (zeolite), hydrophobic solvents (benzene, hexane, hexadecane) [59].

At present, alginatliases, especially endolytic ones, are widely used in the production of alginate oligosaccharides and the production of protoplasts from red and brown algae [60–63]. Alginate oligosaccharides are attracting more and more attention due to their wide application in the food and pharmaceutical industries, as they are characterized by antioxidant, antiproliferative, antitumor activity. Also, they are anticoagulants, stimulate the production of cytokines, exhibit anti-allergic properties. Moreover, alginatliase is promising for use in the treatment of cystic fibrosis due to the decomposition of the polysaccharide biofilm of the pathogen [60–62]. However, most known alginatliases are unstable at elevated temperatures.

Zhu et al. [61] obtained a genetically engineered strain of *Escherichia coli*, which transferred the genes of thermostable alginate lyase from the marine strain of *Flammeovirga* sp. NJ-04. Purified recombinant alginate lyase FsAlgA showed the highest activity (3 343.7 U/mg) at 50 °C and pH 7.0. In addition, this enzyme was characterized by broad substrate specificity and degraded not only sodium alginate but also polymanuronates and polyguluronates.

Alginate lyase AlgC-PL7, synthesized by the halophilic strain *Cobetia* sp. NAP1 appered to be heat-resisting [60]. At 90 °C, the enzyme activity was decreased after 15 min by only 20%, as well as in the presence of 2.0 M NaCl and KCl, the enzyme retained up to 80% of activity.

Not only polymanuronates and polyguluronates were characterized by hydrolytic properties but alginate lyases synthesized by marine bacteria *Vibrio* sp. NJU-03 [62] and *Vibrio furnissii* H1 [63] were as well. The enzyme of strain NJU-03 showed maximum activity at 30 °C and pH 7.0, and strain H1 — 40 °C and pH 7.5.

The ability of the fungus strain *Dendryphiella arenaria* Nicot isolated from red algae to synthesize alginate lyase and fucoidanase was found in a process of growing on a medium with fucoidan and alginate extracted from brown macroalgae *Sargassum latifolium* [64]. Using mathematical methods of experiment planning, the authors determined the optimal composition of nutrient medium for the synthesis of fucoidanase (fucoidan content was 1.5%, NaCl — 1.5%, urea — 0.3%) and alginate lyase (alginate content was 1.5%, NaCl — 4%, NH_4Cl — 0.3%), providing the maximum activity of enzymes in the culture fluid (4 and 24 U/ml, respectively). Subsequent experiments showed that the degree of release of free carbohydrates from polysaccharides under the action of fucoidanase and alginate lyase was 365 mg/g of fucoidan and 439 mg/g of alginate, respectively [64]. The authors noted that these enzymes were promising for use in the production of biofuels from algae.

As a result of agar hydrolysis by agarase, monomers (*D*-galactose, 3,6-anhydro-L-galactose, and L-galactose-6-sulfate) were formed, which could be used for biofuel production [65–67]. Promising is the use of agarase in the production of biologically active agar-oligosaccharides, which are characterized by prebiotic potential, exhibited antitumor, anti-inflammatory, and antioxidant activity, as well as moisturizing and whitening effect in cosmetics. Also, agarase can be used to produce red algae protoplasts, process DNA and RNA from agarose gels, and extract biological substances (carotenoids, vitamins, and fatty acids) [65–67]. Most often agarase is active in the temperature range from 30 to 40 °C. Few enzymes are characterized by high activity at weakly alkaline pH. The high activity of these

enzymes at temperatures above 40 °C is an advantage for the industrial production of agar-oligosaccharides because such temperatures exceed the gelation temperature of agar.

It has been informed of the isolation from marine sediments of the *Acinetobacter junii* PS12B strain, which in the process of cultivation on medium with 0.5% agar at 35 °C and pH 7.0 synthesized agarase with an activity of 0.17 U/ml of culture fluid [65]. In the presence of simple carbohydrates (glucose) in the medium with agar, the enzyme activity was doubled. Later [66], the same authors investigated the physicochemical properties of the purified enzyme and found that agarase synthesized by strain PS12B was thermostable and was characterized by high activity at 50 °C, and maximum activity was observed at 40 °C and pH 8.0.

Not only marine bacteria but also fungi can synthesize agarase. So, the strain *Dendryphiella arenaria* Nicot. under conditions of semi-solid cultivation on a medium containing as a substrate 7.5% biomass of red algae *Palisada perforata*, 0.25% sucrose and 0.08% glucose synthesized agarase with an activity of 7.69 U/ml of culture fluid [67]. Agarase was characterized by high activity in the temperature range from 40 to 80 °C. When heated to 40–50 °C after 30 min, the activity decreased by 25%, and after incubation at 80 °C for 60 min — by 60%. The authors of [67] believed that agarase *D. arenaria* Nicot. could be used with high efficiency to produce biofuels from seaweed.

Enzyme of a wide range of applications is xylanase. In baking, it is used to break down xylan flour with a predominant effect on arabinoxylans, characteristic of endosperm and aleurone layer of the grain, in the production of paper for bleaching cellulose, in animal husbandry to improve the digestibility of animal feed [68, 69].

As a result of screening 493 strains of sea fungi, Dos Santos et al. [68] selected a strain identified as *Aspergillus* cf. *tubingensis* LAMAI31, which was the most active producer of xylanase. Under conditions of growth on medium with xylan xylanase activity was 49.41 U/ml. In the next step, the authors optimized the composition of the nutrient medium, which allowed to increase the xylanase activity to 561.59 U/ml. Xylanase of the strain LAMAI31 was stable in the temperature range of 40–50 °C and pH from 3.6 to 7.0 with an optimum of 55 °C and 5.0, respectively.

The review [69] summarizes the literature data on the potential of sea fungi as an alternative to terrestrial ones for obtaining extracellular enzymes by bioconversion of plant and macroalgae polymer substrates. The authors noted that these biotechnologies might be integrated, because the decomposition of such substrates could produce not only hydrolytic enzymes but plant protein-enriched fungal biomass as well, which in turn was a source of virtually valuable biologically active substances.

Generalized information about enzymes synthesized by marine microorganisms is given in Table 3. Microorganisms isolated from marine habitats capable of synthesizing enzymes that are stable over a wide range of pH and temperature and maintaining high specific activity in contrast to the enzymes synthesized by their traditional terrestrial producers.

Exopolysaccharides

In marine habitats, most microbial cells are surrounded by a layer of extracellular carbohydrate polymers, which are usually exopolysaccharides (EPS). They help microorganisms to survive in adverse conditions by affecting the physicochemical environment near the microbial cell. Some extreme marine environments, such as deep-sea hydrothermal vents, shallow underwater thermal springs, and polar marine habitats, are considered as new sources of EPS-producing bacteria [11, 72].

In 2018, we have published a review [73] on non-traditional producers of microbial EPS, including marine microorganisms (thermo-, psychro-, halophiles and bacteria isolated from deep-water hydrothermal vents). Hereunder we summarized information that appeared or was not published after the publication of the review [73]. In 2018, a review [11] was published on the EPS of marine microorganisms. However, it summarized mostly outdated literature (from the 90s of the twentieth century to 2010–2012), which related mainly to the study of their chemical composition, structure and environmental role, whereas practically valuable properties were considered very briefly.

In our review, we tried to focus on new non-traditional areas of application of EPS of marine microorganisms. This is due to the following reasons. Most currently the known microbial EPSs are characterized by similar functional properties that determine their practical significance. Therefore, it is not surprising that of a large number of isolated, described and studied polysaccharides of

Table 3. **Synthesis of enzymes by marine microorganisms**

Producer	Source of selection	Enzyme	Activity	Properties	Prospects for use	Literature
Enterobacter ludwigii KS92	Siege of the Arctic Fjord	Galactosidase	–	15–35 °C, pH 5–10	Manufacture of lactose-free products at low temperatures	[52]
Geobacillus sp. 4j	Depths of the sea	Amylase	79 U/ml	55–90 °C, pH 4,5–7	Hydrolysis of starch for molasses production	[58]
Flammeovirga sp. NJ-04	Depths of the sea	Alginatliase FsAlgA	3 343,7 U/ml	Optimum 50 °C, pH 7	Treatment of cystic fibrosis. Obtaining alginate oligosaccharides with low molecular weight. Obtaining protoplasts of algae	[61]
Cobetia sp. NAP1	Brown algae	Alginatliase AlgC-PL7	–	Optimum 45 °C, pH 7–8	Obtaining alginate monosaccharides. Biofuel production	[60]
Dendryphiella arenaria Nicot.	Red algae	Alginatliase	24 U/ml	Optimum 40 °C, saccharification 439 mg/g fucoidan	Biofuel production from brown algae	[64]
		Fucoidanase	4 U/ml	Optimum 40 °C, saccharification 365 g/g Fucoidanase	Biofuel production from brown algae	[64]
		Agarase	7,69 U/ml	40–80 °C	Biofuel production from red algae	[67]
Acinetobacter sp. PS12B	Sea sediments	Agarase	45,76 U/ml	Optimum 40 °C, pH 8	Obtaining of agar oligosaccharides, algal hydrolyzate, red algae protoplasts. Biofuel production	[66]
Aspergillus cf. *Tubingensis* LAMAI 31	Sea sponge	Xylanase	561,59 U/ml	30–70 °C, pH 3–7	Pharmaceutical — drugs to improve digestion. Food Industry. Paper and textile industry	[68]
Nigrospora sp. CBMAI 1328	Sea sponge	Laccase	25,2 U/ml	–	Bioremediation, organic catalysis and degradation of xenobiotics. Lignin cleavage. Biosensor systems. Antimicrobial Activity	[70]
Aeromonas caviae CH129	Zooplankton	Chitinase	–	Optimum 37 °C, pH 5	Formation of N-acetylglucosamine, antifungal activity	[71]

Note: «–» — no data.

microbial origin, only some of them (xanthan, gelan, alginate, dextran) are obtained on an industrial scale. Today, in order to enter the market, new polysaccharides must have certain unique properties, thanks to which they can be used in the "free" spheres of rapidly developing industries such as medical, pharmaceutical, cosmetic, environmental.

Most exopolysaccharides synthesized by marine microorganisms are promising for use in medicine and pharmaceuticals [72, 74–78, 80–86], as they show a wide range of biological activity such as follows antitumor [74, 75], antioxidant [72, 75, 78–80], anti-inflammatory [74, 75], anti-adhesive [81, 83], immunomodulatory and antiviral [84, 85], and cryoprotective [76, 77, 82]. Both psychrophilic, mesophilic, and thermophilic strains have been identified among EPS producers.

Most psychrophilic strains were isolated from the polar marine regions of the Arctic and Antarctica. Exopolysaccharides synthesized by microorganisms from polar media are often characterized by unique physicochemical properties and functions. Usually, cold habitats are characterized by frequent temperature changes (freeze-thaw cycles, etc.) [73]. Under these conditions, EPS can act as a cryoprotectant. This property of psychrophiles' EPS makes it possible to consider them as alternative cryoprotectants for long-term storage of suspension cultures [82].

It was found [76] that EPS, synthesized by the psychrophilic γ-proteobacteria *Colwellia psychrerythraea* 34H isolated from Antarctic ice, has a unique structure that mimics antifreeze and prevents recrystallization of ice. Moreover, when cells are frozen to −80 °C, this EPS is a better cryoprotectant than a 10% solution of glycerol. In turn, in [82] it was found that in the presence of 10% of EPS *Pseudomonas* sp. ID1 survival of *Escherichia coli* ATCC 10536 cells after freezing and keeping for 7 days at a temperature of −20 and −80 °C was 36 and 64%, respectively.

The authors [77] showed that the addition of polysaccharide of psychrotolerant Arctic bacteria *Flavobacterium* sp. ASB 3-3 at a concentration of 50 mg/ml increased the number of living cells of the strain *Flavobacterium* sp. ASB 3-3 and *E. coli* DH5α after 2 freeze-thaw cycles 4 times compared to those without EPS. Polysaccharides of psychrophilic and psychrotolerant bacteria had likewise the ability to retain moisture [72], emulsification [77, 82], flocculation [77], and adsorption of metals [79].

During the EPS study of the bacterial strain *Zunongwangia profunda* SM-A87 [72] it was found that after 72 h of dehydration in a chamber with silica gel (relative humidity 43%) the moisture-holding capacity of the polysaccharide strain SM-A87 reached 76%, which was higher than using hyaluronic acid, sodium alginate. According to the authors, such results were due not only to the presence in the EPS of a large amount of glucuronic acid and N-acetylglucosamine, but as was also fucose, which had moisturizing properties. This polysaccharide had antioxidant activity as well [72].

To reduce the cost of the target product the authors of [72] optimized the composition of the nutrient medium (whey — 60.9%, soy flour — 10 g/l and NaCl — 2.9%), and the implementation of the feed process allowed to increase the concentration of EPS of strain Z. *profunda* SM-A87 up to 17 g/l, which was 1.93 times higher than the original technology.

EPS of the psychrotolerant strain *Flavobacterium* sp. ASB 3-3, in addition to cryoprotective, has flocculating and emulsifying properties [77]. Thus, the flocculation activity in a suspension of kaolinite (0.5%) at an EPS concentration of 40 mg/l reached 91.3%, respectively. EPS of *Flavobacterium* sp. ASB 3-3 also emulsified n-hexane (emulsification index 66.3%) and *n*-hexadecane (64.3%) with the same efficiency as sodium dodecyl sulfate.

As for psychrophilic bacteria, the synthesis of exopolysaccharides by thermophilic marine microorganisms is an adaptation mechanism that ensures their survival in adverse environmental conditions.

A representative of thermophilic marine bacteria is the strain *Bacillus licheniformis* T14, isolated from the hydrothermal vein of the island of Panarea (Italy) [81]. This polysaccharide has a wide range of biological activity. Thus, treatment of human peripheral blood mononuclear cells with a solution of polysaccharide (300 μg/ml) led to stimulation of the production of type I cytokines and, as a consequence, inhibition of 77% replication of herpes simplex virus type II [85]. Scientists have also found that this EPS has anticytostatic activity. Thus, fraction 1 EPS of *B. licheniformis* T14, consisting of fructose, fucose, and glucose (1: 0.75: 0.28), at a concentration of 500 ppm increased the LD50 of avarol (cytostatic) from 0.18 to 0.99 mg/ml [84].

It was found that polysaccharides synthesized by *Bacillus licheniformis* T14 [81] and *Pseudomonas stutzeri* 273 [83]

had a unique ability to destroy biofilms of multidrug-resistant strains of pathogenic bacteria *E. coli, Klebsiella pneumoniae, Pseudomonas aeruginosa* and *Staphylococus aureus*. Notably that such properties had not been previously detected in exopolysaccharides formed by traditional producers.

Due to the high content of sulfated and uronic groups, polysaccharides synthesized by mesophilic members of the genus *Bacillus* showed antitumor and anti-inflammatory activity [74, 75].

Thus, polysaccharides synthesized by mesophilic bacteria *Bacillus velezensis* MHM3 [74] at a concentration of 5–80 μg/ml reduced the proliferation of transplanted breast cancer cells (MCF-7) by increasing the expression of genes encoding proapoptotic proteins and reducing the activity of the *Bcl-2* gene, which inhibited the development of apoptosis. The authors suggested that EPS MHM3 might also activate apoptosis by increasing the permeability of the mitochondrial membrane and stimulate the release of cytochrome *c* from mitochondria to the cytosol. The advantage of the strain *B. velezensis* MHM3 was that it synthesized about 6 g/l of polysaccharide, which was many times more than other marine mesophiles.

Selective inhibition of cyclooxygenase (COX) plays a key role in the treatment of inflammatory diseases [75]. Therefore, the development of potent COX inhibitors is an urgent problem. Cyclooxygenases are also involved in lipid metabolism. In particular, they catalyze the oxygenation of polyunsaturated fatty acids, especially arachidonic with the formation of prostaglandin, which is a regulator of inflammatory processes. Prostaglandin can stimulate the growth of tumor cells and suppress the immune response. Also, COX activates carcinogens. In [75] it was found that the exopolysaccharide synthesized by *Bacillus amyloliquefaciens* 3MS inhibited the cyclooxygenase COX-1 and COX-2.

Inhibition of NO formation with selective inhibitory properties of COX-2 activity is considered a promising approach to the treatment of various diseases associated with inflammation, including cancer. EPS of strain 3MS showed antitumor activity against Ehrlich carcinoma [75].

Polysaccharides synthesized by mesophilic members of the *Bacillus* genus had antioxidant activity as well [74, 75]. Thus, the level of neutralization of 2,2-diphenyl-1-picrylhydrazyl radical (DFPG·), hydroxyl radical (·OH) and superoxide anion ($O_2^{-\cdot}$) at the concentration of EPS strains MHM3 and 3MS 500 and 1 000 μg/ml was 52.1–84.4 and 91.44–99.39%, respectively.

Antioxidant activity is also shown by EPS strains of *Halolactibacillus miurensis* T7 (SEEN MKU3) [80].

Also, the EPS of mesophilic bacteria has emulsifying and flocculating properties. Wang et al. [78] isolated a bacterial strain *Aerococcus uriaeequi* HZ, which synthesized EPS with high flocculation activity. With the introduction of 0.2 g of EPS in 100 ml of wastewater, the flocculation index reached 79.90%. The level of neutralization of hydroxyl radical (· OH) and superoxide anion ($O_2^{-\cdot}$) at concentrations of this EPS of 100 and 250 μg/ml, was 45.65 and 67.31%, respectively.

In [79] it was shown that the EPS of the mesophilic bacterium *Alteromonas* sp. JL2810 due to its ability to bind metals, could be used in the processes of biosorption of heavy metals Cu^{2+}, Ni^{2+} and Cr^{6+} in the treatment of mining and industrial waste.

Summarized information about the exopolysaccharides of marine microorganisms is given in table. 4. It is worthwhile to note that, despite the synthesis by marine microorganisms of exopolysaccharides with unique properties, as substrates for their production, carbohydrate raw materials are used. In such case the concentration of the target product is not high enough. Also, such producers require complex mediums with high salt content.

Metabolites with antimicrobial activity

Every year the number of publications on the synthesis of antimicrobial compounds by marine microorganisms increases [87–104]. The largest number of such studies are dated to 2014–2015 [88]. Producers of metabolites with antimicrobial activity are sea fungi of the genus *Beauveria* [89], *Aspergillus* [90, 97, 99], *Penicillium* [91], *Stachybotrys* [93], *Trichoderma* [94], *Engyodontium* [96] and actinobacteria of the genus *Streptomyces* [101–103]. These microorganisms synthesize antimicrobial compounds of different chemical nature, in particular xanthones polyketides [96, 97], terpenoid derivatives [91], butyrolactone [99], anglicycline antibiotics [102, 103] and others.

In most studies, the researchers used the minimum inhibitory concentration as a criterion for antimicrobial activity of metabolites, but in some works they applied

Table 4. **Synthesis of exopolysaccharides by marine microorganisms**

Producer	Source of selection	Cultivation temperature, °C	Source of carbon, g/l	Concentration of EPS, g/l	Physico-chemical properties of EPS		Physiological role, functional properties and prospects of use EPS	Literature
					chemical composition	molecular weight, kDa		
Zunongwangia profunda SM-A87	Seawater	9.8	Serum (60.9%, volume fraction)	17.2	Glucose, mannose, galactose, xylose, fucose, glucuronic acid, non-identifiable, carbohydrate (1:0.84:0.29:0.29: 0.05:0.06:0.21)	3 760	Moisture retaining agent, antioxidant	[72]
Colwellia psychrerythraea 34H	Glacier	4	Peptone, 5	–	N-acetylquinozoamine unit and two galacturonic acid residues are combined with alanine	–	Cryoprotectant	[76]
Pseudomonas sp. ID1	Marine sediments of Antarctica	11	Glucose 20	–	Glucose, galactose, fucose (1:0.5:0.48). Available uronic acids	2 000	Cryoprotectant, emulsifier	[82]
Flavobacterium sp. ASB 3-3	Glacier	20–25	Glycerol, 30	7.25	Glucose, galactose (1:0.43)	–	Emulsifier, flocculant, cryoprotectant	[77]
Aerococcus uriaeequi HZ	Seawater	25	Sucrose, 30	2.34	D-mannose (10.71%) D-Glucose (66.99%)	2.84×10^5	Flocculant, moisture-retaining agent, antioxidant	[78]
Pseudomonas stutzeri 273	Marine bottom sediments	28	Peptone, 10	–	Glucosamine (35.4%), rhamnose (28.6%), Glucose (27.2%), mannose	190	Inhibits the formation of biofilms, antioxidant	[83]
Bacillus velezensis MHM3	Sediments of the coastal zone	25	Sucrose, 50	5.8	Uronic acids and sulfate, glucuronic acid, Glucose, fructose and rhamnose with a molar ratio of 4.00:2.00:1.00:0.13	1 145	Antitumor, anti-inflammatory.	[74]
Bacillus amyloliquefaciens 3MS	Sediments of the coastal zone	28	Glucose, 20	–	Uronic acids (12.3%) and sulfate (22.8%), Glucose, galactose and glucuronic acid in molar ratio 1.6:1.0:0.9	–	Antioxidant, anti-inflammatory and antitumor activity	[75]
Bacillus licheniformis T14	Hydrothermal vent	50	Sucrose, 50	0.366	Fructose, fucose, Glucose (1:0.75:0.28) and traces of galactosamine, mannose	1 000	Antiviral, immunomodulatory and anticytotoxic activity. Inhibits the formation of biofilms	[81, 84, 85]
Halolactibacillus miurensis T7	Place of extraction of sea salt, the coast of India	32	Glucose, 20	2.5	Galactose (61.87%), Glucose (25.17%), xylose, fructose, mannose, rhamnose	–	Antioxidant activity	[80]
Labrenzia sp. PRIM-30	Seawater	32	Dextrose, 10	0.84	Glucose, arabinose, galacturonic acid, mannose (14.4:1.2:1:0.6) Sulfated groups are available 4.76%	269	Antioxidant, emulsifier	[86]
Alteromonas sp. JL2810	Seawater	28	Glucose, 10	0.77	Glucose, mannose, rhamnose	–	Biosorption of metals	[79]

Note: «–» — no data.

the IC_{50} (concentration of the substance that caused the death of 50% of test culture cells) [93, 94].

The authors [89] found that the compound with the trivial name Flavipezine A (aromatic butyrolactone synthesized by *Aspergillus flavipes* AIL8) showed in addition to antibacterial, both antiadhesive activity and the ability to destroy the biofilm of *S. aureus*.

In [102] it was shown that the synthesis of a new anglicycline antibiotic Stremycin A with *Streptomyces pratensis* NA-ZhouS1 strain was observed in response to the so-called "metallic" stress (the presence of heavy metal salts $NiCl_2 \cdot 6H_2O$, $CoCl_2 \cdot 6H_2O$, $ZnSO_4 \cdot 7H_2O$, $CrCl_3 \cdot 6H_2O$, $MnCl_2 \cdot 6H_2O$). The authors found that the action of $NiCl_2 \cdot 6H_2O$ at a concentration of 100 μm activated latent genes clusters responsible for the synthesis of this antibiotic.

The summarized data on the synthesis of secondary metabolites with antimicrobial activity by marine microorganisms is shown in Table 5. As a rule, microorganisms synthesize a complex of such compounds. However, the component of the complex that exhibits the highest antimicrobial activity is shown in Table 5. These data indicates that the vast majority of metabolites are characterized by high antimicrobial activity against a wide range of test cultures, namely minimum inhibitory concentrations range from 0.25 to 16 μg/ml. Slightly lower antimicrobial activity was found for compounds synthesized by *Streptomyces* sp. G278 [103, 104] and *Engyodontium album* DFFSCS021 [97].

To obtain most of the antimicrobial metabolites, the cultivation of marine microorganisms was carried out deeply, and in [89, 96, 97, 99] solid-phase cultivation was used. The use of carbohydrates as a source of carbon nutrition for the production of antimicrobial compounds at present may be a deterrent to the organization of their industrial production.

Metabolites with antitumor activity

The number of identified anti-cancer compounds synthesized by marine microorganisms is increasing every year. Their cytotoxicity has been proven using different tumor cell lines. Thus, in [90, 93, 96, 104–118] it was found that secondary metabolites synthesized by marine microorganisms showed antitumor activity. Stachybocin B, Engidontiumon H and (2R, 4bR, 6aS, 12bS, 12cS, 14a)-4b-deoxy-β-aflatrem were characterized by antimicrobial activity (see Table 5) as well.

Most producers of antitumor compounds are mycelial fungi of the genera *Aspergillus* [90,104–106], *Engyodontium* [96], *Stachybotrys* [93], *Sarcopodium* [108], *Penicillium* [91, 109, 110], *Lasiodiplodia* [111], *Campylocarpon* [112], *Eutypell* [113], *Acaromyces* [116] and others. By the way, some of them are endophytic fungi.

Identified compounds of marine microorganisms have different mechanisms of action on tumor cells *in vitro*. Thus, indole diterpenoid synthesized by *Aspergillus flavus* OUCMDZ-2205 exhibits cytotoxic activity in a model of pulmonary epithelial carcinoma (A549), stopping the cell cycle in phase S [90].

The tetranorditerpenoids wentilactone A and B produced by *Aspergillus wentii* EN-48 were found to induce mitochondrial apoptosis of cancer cells in a model of lung cancer and hepatoma *in vitro*. These compounds activated the Ras/Raf/ERK pathway, which initiated apoptosis and G2/M phase delay during tumor cell proliferation [106, 107]. Xu et al. [105] found that *Aspergillus dimorphicus* SD317 can produce wentilactone A and B. The authors optimized the cultivation conditions of strain SD317. As a result, the concentration of wentilactone A and B in the culture fluid increased by 11 times and was 13.4 and 6.5 mg/l, respectively. The optimal conditions for the synthesis of these compounds were as follows: pH 7.3, salinity 24.5‰, duration of cultivation 27 days at a temperature of 23 °C. Moreover, it was found that introduction of 3% methanol in the nutrient medium could also stimulate the synthesis of wentilactone [105].

Stemphylium globuliferum cells (strain number was not shown) produce altersolanol Q and 10-methyl altersolanol Q [114], *Phomopsis* sp. PM0409092 — altersolanol A [115], which exhibited antitumor activity *in vitro* in a mouse lymphoma model. Their cytotoxic activity was established using 34 human cancer cell lines. The mean IC_{50} and IC_{70} values were 0.005 and 0.024 μg/ml, respectively. Altersolanol A is a kinase inhibitor that induces cell death by apoptosis via a caspase-dependent pathway. The antitumor activity of these compounds is associated with pro-apoptotic and anti-invasive activity, which is manifested in the inhibition of the transcriptional activity of NF-kB [114, 115].

In [109] it was shown that the fungi *Penicillium brocae* MA-231 synthesize brocazines A, B, E and F, which show cytotoxic activity to various cancer cell lines. Brocazines

Table 5. **Synthesis of antimicrobial metabolites by marine microorganisms**

Producer	Source of selection	Source of carbon. g/l	Compound. Type	Test culture	MIC. μg/ml	IC_{50}, μM	Literature
Engyodontium album DFFSCS021	Marine bottom sediments	Rice*. Glucose	Engidontium H Polyketide xanthone	*Escherichia coli* *Bacillus subtilis*	64.0 32.0	–	[96]
Aspergillus versicolor MF359	Sea sponge *Hymeniacidon perleve*	Rice *	5-Methoxides-hydrosterigmatocystine Polyketide xanthone	*Staphylococcus aureus* *Bacillus subtilis*	12.5 3.125	–	[97]
Aspergillus flavipes AIL8	Mangrove plant *Acanthus ilicifolius*	Rice *	Flavi pezine A butyrolactone	*Staphylococcus aureus* *Bacillus subtilis*	8.0 0.25	–	[99]
Aspergillus flavus OUC-MDZ-2205	Shrimp *Penaeus vannamei*	Glucose 10 maltose 20 mannitol 20	(2R.4bR.6aS.12bS. 12cS.14a)-4b-deoxy-β-aflatrem indole diterpenoid	*Staphylococcus aureus*	20.5 мкМ	–	[90]
Stachybotrys sp. MF347	Seawater	Glucose 10	Stachybocin B Bicyclic sesquiterpene	*Staphylococcus epidermidis* *Bacillus subtilis* *Staphylococcus aureus* MRSA	–	1.02 1.42 1.75	[93]
Trichoderma sp. MF106	Seawater	Glucose 10	Trichodin A Pyridines	*Staphylococcus epidermidis* *Bacillus subtilis* *Candida albicans*	–	24.28 27.05 25.38	[94]
Beauveria felina EN-135	Moss	Rice *	Desmethylizalidine C1 cyclohexadepsi peptide	*Escherichia coli*	8	–	[89]
Penicillium brocae MA-231	Mangrove plant *Avicennia marina*	Glucose 20	Penicibrocazin C Diketopi perazine sulfide derivatives	*Staphylococcus aureus* *Micrococcus luteus*	0.25 0.25	–	[91]
Diaporthaceae sp. PSU-SP2/4	Sea sponge	Dextrose-potato broth	Diaportalalazine five-cyclic cytochalasin	*Staphylococcus aureus* MRSA	2	–	[92]
Streptomyces pratensis NA-ZhouS1	Seawater	Starch 20	Stremycin A Angicycline polyketide antibiotic	*Pseudomonas aeruginosa* *Staphylococcus aureus* *Klebsiella pneumonia* *Escherichia coli* *Bacillus subtilis*	16 16 16 16 8–16	–	[102]
Streptomyces sp. A6H	Seawater	–	Vinomycin A1 Angicillin antibiotic	*Staphylococcus aureus*	4	–	[103]
Streptomyces sp. G278	Echino-derms *Holothuria edulis*	Starch 10	**2.5**-Bis (5-tert-butyl-2-benzoxazolyl) thiophene	*Escherichia coli* *Salmonella enterica* *Staphylococcus aureus* *Enterococcus faecalis* *Candida albicans*	64 256 256 256 64	–	[101]

Note: «*» – solid phase cultivation; «–» — no data.

Table 6. **Antitumor activity of secondary metabolites synthesized by marine microorganisms**

Producer	Source of selection	Source of carbon, g/l	Compound. Type	Grafting cell culture	IC_{50}, μM	Literature
Acaromyces ingoldii FS121	Seawater	Dextrose-potato broth	Acaromycin A Anthraquinone derivative	MCF-7 NCI-H460 SF-268 HepG2	6.7 10 7.8 7.3	[116]
*Stemphylium globuliferum**	Mangrove plant *Avicennia marina*	Dextrose-potato agar **	Altersolanol A Anthraquinone derivative	L5178Y BXF T24 RXF 944L PRXF LN-CAP OVXF899L LXF529L GXF251L MEXF462NL	3.4 0.001 0.001 0.001 0.006 0.004 0.052 0.034	[114, 115, 119]
Sarcopodium sp. FKJ-0025	Marine bottom sediments	–	Sarcopodinol B Derivative of hydroquinones	HL-60 Jurkat Panc 1	37 47 66	[108]
Engyodontium album DFFSCS021	Marine bottom sediments	Rice*, Glucose	Engyodontiumone N Xanthone polyketide	U937	4.9	[96]
Aspergillus wentii SD-310	Marine bottom sediments	Potato juiceGlucose	Asperolide E Tetranorlabdan diterpenoid	HeLa, MCF-7 NCI-H446	10.0 11.0 16.0	[104]
Aspergillus dimorphicus SD317	Marine bottom sediments	Dextrose-potato broth	Wentilactone A Tetranorditerpenoid	NCI-H446 NCI-H460	1.9 5.56	[105–107]
			Wentilactone B Tetranorditerpenoid	SMMC-7721	18.96	
Aspergillus flavus OUC-MDZ-2205	Shrimp *Penaeus vannamei*	Glucose,10 Maltose,20 Mannitol 20	(2R,4bR,6aS,12bS, 12cS,14a)-4b-deoxy-β-aflatrem Indole diterpenoid	A549	10	[90]
Eutypella sp. FS46	Marine bottom sediments	Dextrose-potato broth	Scopararane I Pimarane-type diterpene	MCF-7 NCI-H460 SF-268	83.9 13.5 25.3	[113]
Stachybotrys sp. MF347	Seawater	Glucose,10	Stachybocin B Bicyclic sesquiterpene	NIH-3T3 HepG2	16.45 17.87	[93]
Penicillium sp. PR19N-1	Deep waters of Antarctica	–	Eremophilane-type sesquiterpene	HL-60 A549	28.3 5.2	[110]
Penicillium brocae MA-231	Mangrove plant *Avicennia marina*	Dextrose-potato broth	Brocazine A,B,E,F Diketopiperazine derivatives	Du145 HeLa HepG2 MCF-7 NCI-H460 SGC-7901 SW1990 SW480 U251	1.7–11.2 4.3–6.9 2.9–6.4 3.0–9.0 0.89–12.4 2.4–8.0 2.1–6.4 1.2–2.0 3.5–6.1	[109]
Lasiodiplodia sp. 318	Mangrove plant *Exoecaria agallocha*	Rice*	Lasiodiplodine (2,4-dihydroxy-6-nonylbenzoate) Resorcinic acid lactone	MMQ GH3	5.2 13.0	[111]

Table 6 (End)

Producer	Source of selection	Source of carbon, g/l	Compound. Type	Grafting cell culture	IC_{50}, μM	Literature
Campylocarpon sp. HDN13-307	Mangrove plant *Sonneratia caseolaris*	Glucose, 10 Maltose, 20 Mannitol, 20	Campyridone D Pyridone alkaloid	HeLa	8.8	[112]
			Ilicicolin H Pyridone alkaloid		4.7	
Arthrinium arundinis ZSDS1-F3	Sea sponge *Phakellia fusca*	Sorbitol, 20 Maltose, 20	10-phenyl-[12]-cytochalazine Z16 Aminopolyketide	K562 A549 H1975 MCF-7 U937 BGC823 HL60 HeLa MOLT-4	6.2 1.1 14.2 18.5 3 18.8 6.2 3.2 4.1	[117]
Simplicillium obclavatum EIODSF020e	Deep waters	Glucose, 10 Maltose, 20 Mannitol, 20 Starch 0,5	Simplicilliumtide A Linear peptide	HL60	64.7	[118]
			Simplicilliumtide E Linear peptide	K562	39.4	

Note: «*» — strain number is not given; «**» — solid phase cultivation; «–» — no data; IC_{50} — cytotoxicity index; the concentration of the compound that causes 50% lysis of the monolayer of cancer cell.

A and B showed high antitumor activity to the SW480 cell line (IC_{50} 2.0 and 1.2 μM, respectively), while brocazine F — to the DU145 and NCI-H460 cell lines (IC_{50} 1.7 and 0.89 μM in accordance).

Over the past eight years, a number of antitumor compounds synthesized by marine microorganisms have been identified (Table 6). By chemical nature, it is a diverse group of compounds, including tetranorditerpenoids [105–107], scopararane I [113], engidontium H [96], stachybocin B [93], campyridone D [115], anthraquinone derivatives [114–116, 119] and diketopiperazine [109], peptides [118], and others. Their anti-cancer effect has been shown in various models of *in vitro* tumors — breast adenocarcinoma [104, 109, 113, 116, 117], hepatocellular carcinoma [93, 109, 116], leukemia [108, 110, 117, 118], cervical cancer. [104, 109, 112, 117], lungs [90, 110, 117] and others.

Despite a large number of newly identified microbial compounds, only some of them showed better antitumor activity compared to standard anticancer drugs [119]. However, taking into account the chemical diversity of metabolites of marine microorganisms, it could be assumed that rational derivatization could lead to compounds with a wide range of antitumor activity.

Thus, the analysis of literature data showed that marine microorganisms synthesize a wide range of practically valuable enzymes, surfactants, exopolysaccharides, as well as secondary metabolites with diverse biological activity (antimicrobial, antitumor, cytotoxic). However, at present, they can hardly be considered as potential biological agents for use in biotechnological processes. There are several reasons for this.

Firstly, in most studies, researchers do not provide indicators of the synthesis of a target product, and the ability to synthesize it is often established based on qualitative reactions. If in some works the concentrations of certain metabolites (in g/l) are indicated, they are significantly lower than those synthesized by existing industrial strains.

Secondly, marine organisms synthesize practically valuable metabolites growing on expensive carbohydrate substrates (Table 1, 2, 4–6). There are only isolated reports of the use of industrial wastes for example for the synthesis of surfactant lipopeptides (Table 2). Also, high-value complex nutrient media are often used to cultivate marine microorganisms.

Thirdly, in many studies, researchers, have established the ability of marine microorganisms to form a specific target product, do not try to optimize at least the composition of the nutrient medium to increase its synthesis or scale the process of biosynthesis to fermentation equipment.

To predict the possible organization of industrial production with the use of marine microorganisms as producers in the nearest future, it might be biotechnology for

the production of hydrolytic enzymes that decompose plant and algal polymers. The need for such enzymes is due to the use of plant biomass in biofuel production. Also, the genetic potential of marine microorganisms can be used in biotechnology as a source of genes encoding the synthesis of new biologically active substances with unique properties, including antimicrobial and antitumor.

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ПРАКТИЧНО ЦІННІ МЕТАБОЛІТИ МОРСЬКИХ МІКРООРГАНІЗМІВ

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В огляді наведено дані сучасної літератури щодо синтезу грибами, актинобактеріями та бактеріями, виділеними з морських екосистем (морська вода, донні відкладення, поверхня флори та фауни, мангрові біоми, льодовики), практично цінних метаболітів. Морські мікроорганізми синтезують широкий спектр практично цінних ензимів (холодоактивна галактозидаза, агараза, альгінатліаза, фукоїдаза, хітиназа та ін.), поверхнево-активних гліко- та ліпопептидів з емульгувальною, антимікробною та антиадгезивною активністю, екзополісахаридів, а також вторинних метаболітів з різноманітною біологічною активністю (антимікробна, протипухлинна, цитотоксична). Разом з тим використання морських продуцентів у біотехнологічних процесах стримується їхньою невисокою синтезувальною здатністю і великими витратами на біосинтез (складні живильні середовища і дорогі вуглеводні субстрати). У біотехнології морські мікроорганізми можуть бути використані як джерела генів, що кодують синтез нових біологічно активних речовин з унікальними властивостями, зокрема антимікробними та протипухлинними.

Ключові слова: морські гриби, бактерії, біологічно активні речовини.

ПРАКТИЧЕСКИ ЦЕННЫЕ МЕТАБОЛИТЫ МОРСКИХ МИКРООРГАНИЗМОВ

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В обзоре приведены данные современной литературы по синтезу грибами, актинобактериями и бактериями, выделенными из морских экосистем (морская вода, донные отложения, поверхность флоры и фауны, мангровые биомы, ледники), практически ценных метаболитов. Морские микроорганизмы синтезируют широкий спектр практически ценных энзимов (холодоактивная галактозидаза, агараза, альгинатлиаза, фукоидаза, хитиназа и др.), поверхностно-активных глико- и липопептидов с эмульгирующей, антимикробной и антиадгезивной активностью, экзополисахаридов, а также вторичных метаболитов с различной биологической активностью (антимикробная, противоопухолевая, цитотоксическая). Вместе с тем использование морских продуцентов в биотехнологических процессах сдерживается их невысокой синтезирующей способностью и значительными затратами на биосинтез (сложные питательные среды и дорогие углеводные субстраты). В биотехнологии морские микроорганизмы могут быть использованы в качестве источников генов, кодирующих синтез новых биологически активных веществ с уникальными свойствами, в частности антимикробными и противоопухолевыми.

Ключевые слова: морские грибы, бактерии, биологически активные вещества.