==========REVIEWS==========

*The authors dedicate this review to the memory of Corresponding Member of the Russian Academy of Sciences Valery Viktorovich Mikhailov (1952 – 2024), who made a fundamental contribution to the research of marine microorganisms, their systematics and biologically active metabolites*

# MARINE FUNGI: IN SEARCH OF NEW ANTIBACTERIAL DRUGS

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**Abstract.** The review deals with studies of antibacterial secondary metabolites of marine micromycete fungi as an element of a modern strategy for the search for new antibiotics. More than half of the drugs currently used in practice have been isolated from bacteria (Bacteria) and actinomycetes (Actinomycetes), however, the first antimicrobial compounds were isolated from mycelial fungi (Ascomycetes), and it is obvious that their potential has not been exhausted. Marine fungi occupy a separate niche due to the peculiarities of their habitats, which also affect their production of low molecular weight compounds. This paper provides information on the secondary metabolites of marine fungi acting against those bacterial targets aimed by the modern search for new antibiotics and discusses a strategy for investigating the antibacterial activity of marine fungal metabolites.

**Keywords**: *antibiotics, marine fungi, secondary metabolites*

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## INTRODUCTION

At the 68th World Health Assembly in May 2015, the “Global action plan on antimicrobial resistance” was adopted (https://www.who.int/publications/i/item/9789241509763Abbreviations:

NP – National Park. ). This strategy involves studying the mechanisms of the emergence of resistance of pathogenic microorganisms to antibiotics and systemic monitoring of its spread; improving measures to prevent and limit the spread and circulation of pathogens resistant to antimicrobial agents; as well as the development of antimicrobial drugs and alternative methods, technologies and means of prevention, diagnosis and treatment of infectious diseases of humans, animals and plants.

Historically, the first substances with antibacterial activity were natural compounds, whose role in the development of antimicrobial drugs and alternative technologies remains significant today, despite the advances in medicinal chemistry and targeted organic synthesis. Thus, according to data as of December 2018, 45 compounds were participating in clinical trials in the United States, 27 of which were of natural origin (https://www. pewtrusts.org/en/research-and-analysis/data-visualizations/2014/antibiotics-currently-in-clinical-development). According to a review published in 2023, by December 2022, 26 compounds were participating in the first phase of clinical trials, six of which were of natural origin, 25 in the second phase, of which six were also natural, and 11 in the third phase, of which four were natural [1]. The first natural antibiotics were isolated from fungi as early as the late 19th century - in 1893 Bartolomeo Gosio discovered and isolated mycophenolic acid (1) (Fig. 1) from the fungus Penicillium brevicompactum, which inhibited the growth of Bacillus anthracis [2]. Currently, mycophenolic acid is used in the production of mycophenolate mofetil, sold under various trade names, used to prevent transplant rejection, however, this secondary metabolite of micromycete fungi was the first naturally occurring antibiotic isolated in pure form [3].

**Fig. 1** . Structure of mycophenolic acid.

Subsequently, β-lactam antibiotics penicillin and cephalosporin C were obtained from micromycete fungi *Penicillium rubens* and *Acremonium chrysogenum* , and pleuromutilin (the first of which was lefamulin) was isolated from the terrestrial basidiomycete fungus *Clitopilus passeckerianus* . However, more than half of currently used antibacterial drugs are derived from compounds isolated from mycelial actinomycetes and other bacteria [4]. Nevertheless, due to the peculiarities of the relationships between fungi and bacteria in microbial communities [5] , where bacteria almost always predominate, mycelial fungi (both terrestrial and marine habitats) continue

to be considered as a source of individual compounds with antibacterial activity. In this regard, the purpose of this review is to evaluate the achievements and prospects of searching for new antibacterial agents among marine mycelial fungi. The authors do not include antitumor antibiotics and compounds with antimycotic action in the review, as this would significantly increase its volume.

## MARINE FUNGI AS PRODUCERS OF ANTIBACTERIAL COMPOUNDS

Secondary low-molecular-weight metabolites play an important role in the adaptation of fungi-producers to their habitat conditions, as they are the final link in the chain of response to biotic and abiotic factors [6]. Interest in studying secondary metabolites of fungi emerged in the late 1980s. According to the Natural Products Atlas database (https://www.npatlas.org), the first wave of intensification in research on metabolites from fungi of all habitats was observed in 2012–2015, and the next one in 2017–2020 [7], with a doubling in the number of annually published compounds – from 655 in 2011 to 1236 in 2020. The number of new compounds meeting the criterion of maximum similarity index <0.5 (Dice similarity, Morgan fingerprinting with radius 2), ranged from 22 in 2020 to 53 in 2018. Analysis of data on 55 817 compounds isolated from marine and terrestrial microorganisms [8] showed that 14.3% of compounds from marine microorganisms are unique, and this percentage increases when it comes to Ascomycota fungi – from marine isolates of which almost a quarter of new compounds (23%) have been isolated. The authors of this work also concluded that the probability of discovering unique compounds is less influenced by depth and geographical location of the microorganism collection site, and more by the selection of marine-specific and understudied species [8].

Periodically, discussions arise about which fungi should be correctly considered marine. One of the proposed broad definitions suggests that a marine fungus is any fungus that is repeatedly isolated from a marine environment because: 1) it is capable of growing and/or forming spores (on substrates) in a marine environment; 2) it forms symbiotic relationships with other marine organisms; or 3) it has been proven to adapt and evolve at the genetic level or is metabolically active in the marine environment [9]. There is an opinion that according to these criteria, fungi associated with mangrove plants (growing on the seashore and experiencing the effects of tides) are not considered truly marine; however, this issue has long been a subject of debate, and most

reviews on metabolites of marine fungi also describe metabolites of fungi associated with mangroves. In the mid-20th century, the study of secondary metabolites of marine fungi was limited by methods of strain isolation and laboratory cultivation, but since the 1980s, active research on these compounds began. In 2019, metabolites from marine fungi accounted for almost half of all newly described marine natural compounds, whereas in 2015, half as many were isolated (although still more than from any other marine sources) [10].

A significant portion of secondary metabolites from marine fungi possess anti-inflammatory [11] or antitumor [12] activity, but their antimicrobial action attracts the greatest interest. From 1998 to 2019, 207 new compounds with antibacterial activity were isolated from marine fungi of various origins [13]. The intensification of research in this field can be traced using the example of fungi isolated from marine bottom sediments: during the ten-year period from 2005 to 2015, only 346 compounds were described, of which 24 had antimicrobial activity [14-17]; during the subsequent five-year period (2016-2020), 246 compounds were described, and 57 of them demonstrated antibacterial activity [18]. Among the new secondary metabolites of marine fungi with antimicrobial action isolated from 1998 to 2019, polyketides predominated (81.2%), terpenoids and steroids accounted for 11.4%, while nitrogen-containing and halogen-containing compounds made up 33.4 and 4.8% respectively [19]. From 1991 to 2023, 336 both cyclic and linear peptides were isolated from marine fungi, and about 70 of them showed antibacterial activity [20]. More than 100 macrolides from marine fungi are known [21], some of which possess antibacterial activity [22]. Also, from 2015 to 2020, 35 new antimicrobial alkaloids were described [23]. However, a more rigorous analysis [24] leads to the conclusion that only 108 compounds isolated from marine fungi can be considered promising – and none of them has been studied sufficiently to proceed to clinical trials.

## SECONDARY METABOLITES OF MARINE FUNGI WITH ANTIMICROBIAL ACTION

By the beginning of 2024, there were 138 international nonproprietary names and 540 trade names of antibiotics registered in the Russian market, including combination drugs [25], which from the perspective of their chemical structure are β-lactams, macrolides, tetracyclines, aminoglycosides, sulfonamides, quinolones, peptides, and others. Based on their mechanism of action, they can be divided into inhibitors of cell wall synthesis, membrane structure functions , protein synthesis on ribosomes, nucleic acid functions, as well as inhibitors of microbial

metabolism [26]. Below are examples of drugs belonging to each group, and some secondary metabolites of marine fungi that show activity against the same targets as these drugs.

*Impact on bacterial cell wall synthesis*

Bacterial cell wall synthesis is inhibited by penicillins (penicillin, ampicillin, oxacillin), cephalosporins (cefazolin, cefotaxime, ceftriaxone, cefepime), carbapenems (imipenem), glycopeptides (vancomycin, teicoplanin) [27], nisin, moenomycin.

Penicillin F ( **2** ) (Fig. 2) was isolated from the fungal culture *Penicillium notatum* by Alexander Fleming in 1928, and humanity will soon be celebrating the centenary of this greatest discovery. The β-lactam ring determines the antibacterial biological activity not only of penicillins but also of other clinically important compounds that make up the β-lactam antibiotic family [28]. The structural subclasses of this family include cephalosporins, cephamycins, clavulanic acid, nocardicins, monobactams, and carbapenems. An important event in the history of β-lactams was the isolation by Giuseppe Brotzu in 1945 of the cephalosporin C ( **3** ) (Fig. 2) producing fungus *Cephalosporium acremonium* in Cagliari (Sardinia, Mediterranean Sea) [28], however, subsequent subfamilies of β-lactams are secondary metabolites of terrestrial bacteria. Analysis of the genomic DNA of the marine fungus *Kallichroma tethys* , conducted in 2003, revealed two genes – *pcbAB* and *pcbC* , encoding proteins homologous to penicillin biosynthesis enzymes, but attempts to isolate penicillin-related compounds from the fungal culture were unsuccessful [29].

**Fig. 2** . Structures of fungal β-lactam metabolites.

Enniatins - low molecular weight cyclohexapeptides capable of destroying bacterial cell walls through ionophore action, were first isolated from fungi of the genus *Fusarium* , associated with various sources, including marine algae, and later from fungi of the genera *Verticillium* and *Halosarpheia* [30]. To date, about 30 compounds of this group are known, which consist of three N-methylated amino acid residues, usually valine, leucine, and isoleucine, and three hydroxy acid residues, predominantly hydroxyisovaleric acid [31]. The drug fusafungin, consisting of a complex of enniatins, was actively used to treat upper respiratory tract infections (in Russia, fusafungin is known as the spray "Bioparox"), but in 2016 it was banned by the European Medicines Agency, as in some cases it caused severe allergic reactions such as bronchospasm [4]. However, it was

recently shown that enniatin B ( **4** ) (Fig. 3) is capable of inhibiting the formation of *Candida albicans* biofilms [32], which opens new possibilities for its therapeutic use.

*Effects on membrane structure functions*

Membrane structure functioning is influenced by lipopeptide antibiotics (daptomycin and polymyxins) [26]. Lipopeptides produced by fungi can be divided into structural groups such as cyclic depsipeptides, peptaibiotics (peptaibols, lipoaminopeptides, and lipopeptaibols), non-depsipeptide cyclic lipopeptides, and non-peptaibol linear lipopeptides [33]. Cyclohexadepsipeptides of the isaridin group, for example, desmethylisaridin C1 ( **5** ) (Fig. 3), which showed antibacterial activity, were isolated from the marine strain *Beauveria felina* EN-135 [34]. A cyclic pentadepsipeptide was isolated from the marine fungus *Alternaria* sp. SF-5016 [35], and a number of peptaibols, such as trichorzianin 1938 ( **6** ) (Fig. 3), from the marine fungus *Trichoderma atroviride* (NF16) [36]. In total, more than 200 compounds of this class have been described to date; however, it is only known that they can affect the growth of test bacterial strains, while their effects on membrane functioning have not been studied.

**Fig. 3.** Structures of peptide metabolites from marine fungi.

*Inhibition of protein synthesis on ribosomes*

Suppression of ribosomal protein synthesis is the main mechanism of action of aminoglycoside antibiotics (including gentamicin, tobramycin, streptomycin, kanamycin), tetracyclines (tetracycline, doxycycline), macrolides (erythromycin, azithromycin), streptogramins (including pristinomycin, dalfopristin, quinupristin), amphenicols (chloramphenicol) [27], as well as oxazolidinones (tedizolid, linezolid), pleuromutilins (lefamulin, retapamulin), lincosamides (lincomycin, clindamycin), and thiostrepton [26].

Fusidic acid ( **7** ) is a fusidane-type triterpenoid (Fig. 4) isolated from the fungus *Acremonium fusidioides* . This compound was discovered in the early 1960s by researchers at Leo Pharma (Germany) during testing of strains from the Centraalbureau voor Schimmelcultures, and the producing strain itself was obtained by Japanese mycologist Keisuke Tubaki from wild monkey excrement [37]. It has been established that fusidic acid affects protein synthesis by inhibiting the dissociation of elongation factor G from the ribosome. After a series of

complaints from Irish miners about side effects, fusidic acid was "taken out of service," but in the early 2000s, a number of studies, primarily the work of Falagas M.E. et al. [38], generated a new wave of attention to it. Currently, fusidic acid is industrially isolated from the culture liquid of the fungus *Fusidium coccineum* and is produced in various dosage forms. This antibiotic is also produced by some other fungal strains, including the marine fungus *Stilbella aciculosa* KMM 4500 [39].

**Fig. 4.** Structures of triterpenoid metabolites from marine fungi.

Other known steroid antibiotics are helvolic acid ( **8** ), cephalosporin P1, and viridian [37], but only fusidic acid is currently available as a commercial preparation. Helvolic acid ( **8** ) (Fig. 4) has been known as an antibiotic since 1943, when it was isolated from the fungal culture *Aspergillus fumigatus, mut. helvola Yuill* [40]. This fusidane-type triterpenoid is mainly isolated from various strains of the fungus *A. fumigatus* and is considered one of its virulence factors [41]. A series of new helvolic acid derivatives were isolated from the marine fungus *A. fumigatus* HNMF0047, which showed more pronounced activity against *Streptococcus agalactiae* than the antibiotic tobramycin [42].

The first representative of the pleuromutilin class of antibiotics - diterpene compounds containing a unique 5/6/8-tricyclic skeleton in their structure, was isolated from the terrestrial basidiomycete *Clitopilus passeckerianus* [43]. Production of such diterpenoids is not characteristic for micromycetes, including marine ones [44], however, these organisms synthesize other diverse diterpenes.

Oxazolidinones are a relatively new class of antibiotics, the first representative of which, linezolid, was approved for use in 2000, and the second - tedizolid - in 2014. These 2-oxazolidinones were obtained synthetically [45], however, compounds containing oxazolidinone fragments in their structure are produced by marine sponges [46, 47], some terrestrial plants [48, 49], as well as streptomycetes [50] and cyanobacteria [51]. Among the metabolites of marine fungi, the most structurally similar are the 2,4-pyrrolidinedione alkaloid harzianopyridone ( **9** ) [52] and its derivatives. It has been shown that harzianopyridone (Fig. 5) acts on the cell membrane of

*Staphylococcus pseudintermedius* [53], possibly due to its ability to bind calcium ions and thus affect calcium signaling [54], but its effect on protein synthesis in ribosomes has not been studied.

**Fig. 5** . Structures of harzianopyridone and some fungal 6/6/5-tricyclic polyketides.

Chlorocyclopentadienylbenzopyrone coniotyrion ( **10** ) (Fig. 5), capable of inhibiting ribosomal protein S4 and thereby stopping translation, was isolated from the terrestrial fungus *Coniothyrium cerealis* [55], and later from the marine strain *Neosetophoma samarorum* [56]. The structurally similar acruchinone C ( *Asteromyces cruciatus* , along with coniotyrinones B and D, which possess antibacterial activity, but information about the effect of these compounds on ribosomal protein synthesis is not yet available [57]. **11** ) (Fig. 5) was isolated from the marine fungus

*Inhibition of DNA and RNA synthesis*

Research on the bacterial replication mechanism has revealed certain aspects that have great potential as targets for medicinal drugs [58]. Quinolones, one of the most extensive groups of synthetic antibiotics used in practice, are aimed at suppressing DNA replication. Four generations of quinolones are known: 1) non-fluorinated quinolones (nalidixic, oxolinic, pipemidic acids), 2) gram-negative fluoroquinolones (norfloxacin, ofloxacin, pefloxacin, ciprofloxacin, and others), 3) respiratory fluoroquinolones (levofloxacin, sparfloxacin, and others), 4) respiratory-antianaerobic fluoroquinolones (moxifloxacin) [59]. Their mechanism of action is based on the inhibition of bacterial enzymes – DNA gyrase, topoisomerases II and IV. Natural macrolide antibiotics ansamycins (including rifamycin) suppress the activity of DNA-dependent RNA polymerase; tuakumycins (including fidaxomycin), which bind to bacterial DNA-dependent RNA polymerase, inhibit the initiation of bacterial RNA synthesis; azalides (azithromycin, metronidazole) competitively inhibit nucleic acid synthesis [26].

Quinolones currently used in practice are synthetic, however, it is known that compounds of this class are produced by plants and fungi [60], including marine ones. For example, quinolactacin E ( **12** ) (Fig. 6), isolated from the culture of the fungus *Penicillium* sp. SCSIO41015,

associated with a marine sponge [61]. However, the ability of the isolated compounds to inhibit nucleic acid synthesis has not been studied.

Several classes of natural inhibitors of bacterial DNA gyrases are known: aminocoumarins, simocyclinones, cyclothialidines, catechin group polyphenols [62], however, the vast majority of inhibitors of various bacterial DNA gyrases are of synthetic origin. It has been shown that the natural anthraquinone emodin ( **13** ) (Fig. 6), produced by plants and fungi (including marine ones [63]), is capable of partially inhibiting DNA gyrases of *S. aureus* and *Escherichia coli* , while its synthetic halogenated derivative haloemodin possessed greater efficacy [64]. Such well-known natural DNA gyrase inhibitors as novobiocin ( **14** ) (Fig. 6), chlorobiocin, and coumermycin A1 were isolated from streptomycetes [65], but fungi are also capable of producing various coumarins, including aminocoumarins [66], so it is obvious that the potential of fungal secondary metabolites, including marine ones, as inhibitors of bacterial DNA gyrases, has not yet been fully revealed.

**Fig. 6** . Structures of secondary metabolites from marine fungi - inhibitors of nucleic acid synthesis in bacteria.

Another potential target for developed drugs (besides DNA gyrase and replicative polymerases) is the subcomplex - primosome, consisting of DnaB/C helicase and DnaG primase. The bicyclic macrolide Sch 642305 ( **15** ) (Fig. 7), isolated from the soil fungus *P. verrucosum* , inhibited DNA primase of *E. coli* [67]. This activity was also possessed by the octaketide cytosporone D ( **16** ) (Fig. 7), produced by fungal cultures of *Cytospora* sp. and *Diaporthe* sp. [68] and *Phomopsis* sp. [69]. However, there are currently no data on clinical trials of DNA primase inhibitors [70].

**Fig. 7.** Structures of secondary metabolites from marine fungi - inhibitors of bacterial DNA primases.

*Effect on the quorum sensing*

Some time ago, in the search for new antibiotics, close attention began to be paid to substances affecting the formation or functioning of bacterial biofilms, recognising their

importance in the development of certain infectious diseases [71, 72]. Depending on the population density and environment, bacteria can be found in planktonic form and biofilms. The behaviour of the bacterial population is controlled by a global regulatory system, the quorum sensing (QS) system, which is regarded as a cell density-dependent and environment-dependent regulatory pathway to ensure intercellular communication [73].

The QS system in *S. aureus* and other gram-positive bacteria is controlled by the Agr-like system [74], which includes the regulatory protein AgrA and the sensory protein histidine kinase AgrC, which, under the influence of peptide autoinducers, initiates the regulatory expression of RNA III. At high cell density, RNA III triggers the expression of a large number of extracellular toxins, including α-hemolysin. In addition to toxin production, the formation of biofilm phenotype in *S. aureus* cells is under QS control, which involves accumulation-associated proteins (Aap); surface-binding proteins Spa and SasG; fibronectin-binding proteins FnbA and FnbB; and cell wall-anchored proteins (CWA) that facilitate adhesion [75]. The covalent attachment of these proteins to the bacterial cell wall is provided by the membrane-bound transpeptidase sortase, which has several isoforms, among which sortase A [EC 3.4.22.70] is of primary importance [76].

Both natural and synthetic inhibitors of the Agr system have been actively studied since its discovery in the early 1990s. By 2019, approximately 20 compounds isolated from plants and microorganisms were known to be capable of directly affecting the Agr system [77, 78]. Antagonistic action on the staphylococcal Agr system has been shown for apicidin ( **17** ) (Fig. 8), a cyclic tetrapeptide from the terrestrial fungus *Chaetosphaeriaceae* sp. [79], and ambuic acid ( **18** ) (Fig. 8), isolated from various fungi, including representatives of the genera *Monochaetia* and *Pestalotiopsis* [80]. The cyclic peptide avellanin C was isolated from the fungus *Hamigera ingelheimensis* , and its effect on the Agr system of *S. aureus* was demonstrated using a transformant with a plasmid containing the luciferase gene under the promoter of the *agr* P3 gene [81]. The effect on the Agr system of *S. aureus* by the polyhydroxyanthraquinone ω-hydroxyemodin from the endophytic fungus *P. restrictum* [82], as well as a number of other polyhydroxyanthraquinones isolated from *P. restrictum* [83].

**Fig. 8.** Structures of fungal metabolites - antagonists of the Agr system of *Staphylococcus aureus.*

The antimicrobial activity of the anthraquinone emodin ( **13** ) and its effect on biofilm formation by various bacterial strains has been studied very actively [84]. It has been established that emodin not only inhibits the growth of *S. aureus* [85], but also affects biofilm formation and expression of the genes *icaA, icaD, srrA, srrB* and *RNAIII* [86]. Another anthraquinone, aloe-emodin, also affected biofilm formation by *S. aureus* [87]. In a mouse model *in vivo* , the promise of using emodin in the treatment of acute osteomyelitis caused by a methicillin-resistant strain of *S. aureus* [88] was demonstrated. Emodin and its derivatives are known primarily as plant metabolites [89], however, polyhydroxylated anthraquinones are also fungal metabolites [90], and marine fungi often become sources of new compounds of this class [91]. Thus, new acruchinones A-C were isolated from the obligate marine fungus *Asteromyces cruciatus* KMM 4696, with acruchinone C ( **11** ) (Fig. 5) being the first discovered anthraquinone with a 6/6/5-skeleton [57]. Acruchinone A ( **19** ) significantly inhibited biofilm formation by *S. aureus* , increased keratinocyte viability, and accelerated keratinocyte proliferation and migration in experiments with HaCaT line keratinocytes infected with a suspension of *S. aureus* bacteria.

Due to the special role of sortase A in biofilm formation and, consequently, the pathogenicity of *S. aureus* , this enzyme is considered a promising target for the search for new antistaphylococcal drugs [92]. Among marine fungal metabolites, inhibitors of sortase A have been identified: the polyketide aspermitin A ( **20** ) (Fig. 9) [93], penta- and hexapeptides [94], naphthoquinone herqueidiketal ( **21** ) (Fig. 9) [95]. Very recently, inhibitory activity against sortase A was shown for asterripeptides A, B, and C ( **22** ) - new tripeptides with an unusual cinnamic acid fragment in their structure (Fig. 9), isolated from the marine fungus *A. terreus* LM5.2 [96]. Inhibition of sortase A by a number of new chlorine-containing polyketides has also been demonstrated, including acrucipentin E ( **23** ) (Fig. 9) from the marine fungus *Asteromyces cruciatus* KMM 4696 [97] and a new cyclopianic diterpene 13-epi - conidiogenone F ( **24** ) (Fig. 9) from the marine fungus *P. antarcticum* KMM 4670 [98].

**Fig. 9** . Structures of secondary metabolites from marine fungi - sortase A inhibitors.

The cereberoside flavuside B ( *P. islandicum* not only inhibited sortase A activity and biofilm formation of **25** ) (Fig. 10) isolated from the marine fungus *S. aureus* , but also in experiments with HaCaT keratinocyte cell line infected with *S. aureus* bacteria, it increased

keratinocyte viability, reduced the level of apoptosis, inflammation markers, and restored the passage of infected keratinocytes through cell cycle stages [99].

**Fig. 10** . Structure of flavuside B.

The QS-system of gram-negative bacteria is organized based on small peptides called acylhomoserine lactones (AHLs). Typically, this system consists of three components: 1) a cytoplasmic protein AHL-synthase of the LuxI family; 2) an AHL-sensitive DNA-binding transcription regulator belonging to the LuxR family; and 3) acylhomoserine lactone, which contains a conserved homoserine lactone ring connected by an amide bond to a variable side chain [100]. To study the effects of compounds on the QS-system of gram-negative bacteria, a test system based on *Chromobacterium violaceum* is actively used, based on the change in coloration of *C. violaceum* in response to the appearance of acylhomoserine lactones in the medium [101] . Using such a biosensor, anti-QS activity has been established for alternariol monomethyl ether from the marine fungus *Alternaria* sp., kojic acid from a marine strain of *Aspergillus* sp., meleagrin ( **26** ) (Fig. 11) from *P. chrysogenum* , alterporriole E ( **27** ) (Fig. 11) from *Alternaria porri* , alterlactone from *Alternaria* sp., and altersolanol from *Alternaria solani* [102]. The QS-system of gram-negative bacteria is also inhibited by aculenes C–E, penicitor B, and aspergillumarin A ( **28** ) (Fig. 11) and B from the fungus *Penicillium* sp. SCS-KFD08, associated with the marine worm *Sipunculus nudus* [103].

**Fig. 11.** Structures of secondary metabolites from marine fungi – inhibitors of the QS-system of gram-negative bacteria.

Thus, despite the large number and structural diversity of secondary metabolites isolated from marine fungi, only a small number of them are studied in detail regarding any bacterial targets. In most cases, only the effect on the growth of bacterial cultures is evaluated. Secondary metabolites of marine fungi with established specific antibacterial activity are listed in Table 1.

**Table 1**. Secondary metabolites of marine fungi with known mechanism of action

| No. | Compound | Marine fungus-producer | Reference |
|---|---|---|---|
| | *Effect on bacterial cell wall construction* | | |
| 1 | Cephalosporin C | *Cephalosporium acremonium* | |
| 2 | Enniatins | fungi of genus *Fusarium* | [30] |
| | *Effect on membrane structure functions* | | |
| | | | |
| | *Inhibition of protein synthesis on ribosomes* | | |
| 3 | Fusidic acid | *Stilbella aciculosa* KMM 4500 | [39] |
| 4 | Helvollic acid and its derivatives | *Aspergillus fumigatus* HNMF0047 | [42] |
| 5 | Conithyrione | *Neosetophoma samarorum* | [56] |
| | | | |
| | *Inhibition of DNA and RNA synthesis* | | |
| 6 | Emodin | strains of various fungal species, including marine ones | [64] |
| 7 | Cytosporone D | *Cytospora* sp. and *Diaporthe* sp., *Phomopsis* sp. | [68], [69] |
| | | | |
| | *Effect on quorum sensing system and biofilm formation* | | |
| | Emodin | strains of various fungal species, including marine ones | [86] |
| 8 | Aloe-emodin | | [87] |
| 9 | Acruchinones A–C | *Asteromyces cruciatus* KMM 4696 | [57] |
| 10 | Aspermitin A | | [93] |
| 11 | Penta- and hexapeptides | | [94] |
| 12 | Herqueidiketal | | [95] |
| 13 | Asterripeptides A-C | *Aspergillus terreus* LM5.2 | [96] |
| 14 | Chlorinated polyketides | *Asteromyces cruciatus* KMM 4696 | [97] |
| 15 | 13epi *epi* -Conidiogenone F | *Penicillium antarcticum* KMM 4670 | [98] |
| 16 | Flavuside B | *Penicillium islandicum* | [99] |
| 17 | Alternariol monomethyl ether | *Alternaria* sp. | [102] |
| 18 | Kojic acid | *Aspergillus* sp. | [102] |
| 19 | Meleagrin | *Penicillium chrysogenum* | [102] |
| 20 | Alterporriol E | *Alternaria porri* | [102] |
| 21 | Alterlactone | *Alternaria* sp. | [102] |
| 22 | Altersolaniol | *Alternaria solani* | [102] |
| 23 | Aculenes C, D and E | *Penicillium* sp. SCS-KFD08 | [103] |
| 24 | Penicitor B | *Penicillium* sp. SCS-KFD08 | [103] |
| 25 | Aspergillumarine A and B | *Penicillium* sp. SCS-KFD08 | [103] |

## METHODS OF CULTIVATING MARINE FUNGI FOR OBTAINING NEW ANTIMICROBIAL SECONDARY METABOLITES

Co-cultivation of two or more fungal strains is a rather effective method for obtaining new compounds with antimicrobial properties. When two fungi come into contact in culture, a MAPK-dependent cascade of reactions known as cell wall integrity (CWI) stress is activated. This type of stress [104] can lead to changes in the production of melanin group antioxidants, mycotoxins, and antibiotics by fungi, such as gliotoxin, ACT-toxin, beauvericin, fusaric acid, fumonisin B1, penicillin, triacetoxyscirpenol C, ganoderic acid, and other metabolites. Also, the production of a gliotoxin derivative increased in the co-culture of two marine fungi *Aspergillus fumigatus* KMM4631 and *Asteromyces cruciatus* KMM4696 [105].

Between 2009 and 2019, 59 new compounds with various biological activities were obtained as a result of co-cultivation of marine fungi [106]. A new alkaloid with antimicrobial activity, aspergicin ( **29** ) (Fig. 12), was isolated from a co-culture of two marine endophytic fungi of the genus *Aspergillus* [107]. New seco-penicitrinol A ( **30** ) (Fig. 12) and penicitrinol L, which showed significant antimicrobial activity, were found in a co-culture of marine fungi *A. sydowii* EN-534 and *P. citrinum* EN-535 [108]. From the joint culture of *P. sajarovii* KMM 4718 and *A. protuberus* KMM 4747, a new polyketide sajaroketide A ( **31** ) (Fig. 12) was isolated, which not only exhibited antimicrobial activity against *S. aureus* and *E. coli* , but also proved effective in an *in vitro* model of infectious myocarditis, when H9c2 line cardiomyocytes were cultured together with *S. aureus* bacteria [109].

The production of low-molecular-weight compounds with antibacterial properties can also be stimulated by co-cultivation of fungi and bacteria. For example, cultivation of the marine strain *A. versicolor* with bacteria *Bacillus subtilis* led to the isolation of a new cyclic pentapeptide – cotteslosin C ( **32** ) (Fig. 12), new aflaquinolones and anthraquinones, as well as a several-fold increase in the production of versicolorin B, averufin, and sterigmatocystin [110].

**Fig. 12** . Structures of antibacterial low-molecular-weight compounds obtained by co-cultivation of marine fungi with other microorganisms.

## CONCLUSION

Since 2010, about twenty new antibacterial drugs have been introduced into global clinical practice: tetracyclines omadacycline and eravacycline; aminoglycoside plazomicin; quinolones nemonoxacin, finafloxacin, and delafloxacin; drugs used both in Russia and other countries: fifth-generation cephalosporins ceftolozane and ceftaroline fosamil; semi-synthetic lipoglycopeptide dalbavancin; second-generation oxazolidinone tedizolid [111]. In April 2024, a new synthetic drug "Ftortiazinon" was registered in Russia, which by its chemical structure is a thiodiazinone and can specifically inhibit motility, toxin secretion, invasion, colonization, and biofilm formation by pathogenic bacteria [112, 113]. Thus, modern trends in research on new antibacterial drugs and methods of their application, such as targeted therapy aimed at new targets, including virulence factors, potentiation of already known drugs by suppressing the protective systems of pathogens, involving the immune system in confrontation with them, are bringing practical results [114].

Obviously, diverse secondary metabolites of marine fungi, isolated each year, can make a significant contribution to the discovery of new antibacterial drugs. The limiting factors here are the small quantities of isolated compounds, instability of their production by some strains, and lack of research strategy. Nevertheless, biotechnological approaches to large-scale cultivation of producer strains, selection of cultivation conditions for marine fungi leading to the highest yield of target compounds, and targeted study of biological activity of isolated compounds in relation to various aspects of pathogenic bacteria can overcome the limiting factors and discover new candidate compounds.

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## ETHICS DECLARATION

This article does not contain any studies involving humans or animals as research subjects.

## CONFLICT OF INTERESTS

The authors declare no conflict of interest.

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