Antimicrobial Properties and the Effect of Temperature on the Formation of Secondary Metabolites in Psychrophilic Micromycetes

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Abstract—The ability of representatives of psychrotolerant micromycetes to produce antimicrobial compounds was studied. A promising producer of antibiotics, *Penicillium vulpinum* KPB F-290, was selected (from 98 cultures) as a result of the screening. The producer was active against opportunistic fungi and bacteria. The isolated active fractions can be attributed to the group of antimicrobial compounds, including β-lactam antibiotics and peptides.

Keywords: antimicrobial compounds, psychrotolerant micromycetes, antibiotics

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INTRODUCTION

An urgent task of medical biotechnology and pharmacology is the search for and isolation of new natural antimicrobial compounds that can serve as the basis for the development of drugs. Antimicrobial substances that are effective against pathogens resistant to antibiotics used in medical practice are of particular interest [1–3].

Various strategies were used to search for natural biologically active compounds in different periods: from traditional phenotypic screening to the introduction of advances in genomics, transcriptomics, proteomics, metabolomics, and other technologies [4].

In the last decade, new compounds with biological activity have been sought among producers isolated from extreme ecosystems: seas, saline soils, and other sources [5]. Over the past 10–15 years, more than 20000 such compounds have been isolated and characterized [6, 7].

To date, there is information on promising antimicrobial metabolites of microorganisms isolated mainly in places with a tropical climate; however, there is relatively little information on the metabolites of inhabitants of cold places in the Arctic, Antarctic, and the bottom waters of deep-water lakes [8].

According to the literature data, the antimicrobial potential of isolates of cold habitats was partially studied in prokaryotes [9], while almost no such studies have been carried out with regard to micromycetes until now. Micromycetes of cold habitats may turn out to be an undeveloped, valuable source of new producers, since their survival in polar conditions requires high adaptability and resistance to many stresses. These include poor nutrient availability, significant UV radiation, prolonged exposure to frequent fluctuations in temperature towards negative values, etc. All of the above factors together contribute to the evolutionary adaptation of the so-called psychophilic microorganisms and the synthesis of specific metabolites in them [10, 11]. A number of secondary metabolites with antimicrobial activity were isolated from isolates of Arctic and Antarctic fungi [12, 13]. Among them, five new bioactive asterric acid derivatives were found. The producer is the Arctic ascomycete *Pseudo- gymnoascus* sp. The compounds showed antifungal activity against *Aspergillus fumigatus*, and some showed antimicrobial activity against gram-positive and gram-negative bacteria [14].

*Penicillium griseofulvum* isolated from the soils of Greenland produces a number of secondary metabolites, including griseofulvin, fulvic acid, myceliamide, roquefortine C, roquefortine D, chanoclavin I,
and elymoclav. All substances exhibited antimicrobial activity [15]. In [16], new compounds with a unique structure were isolated in Spiromastix sp. from deep-water sediments of the South Atlantic Ocean. It was established that the Arctic isolate of *Penicillium nalgiovense* is able to synthesize amphotericin B [17], while the strain *Geomyces* sp. 2481 synthesizes antymycotic geomycin B and antibacterial component geomycin C [18]. A psychrotolerant strain, *Penicillium algidum*, synthesizes a new cyclic nitropeptide called psychrophilin D [19], which is active against p388 mouse leukemia cell lines. Another psychrotolerant isolate of the micromycete *Penicillium* sp. PR19 N-1 produces rare new sesquiterpene compounds of the eremophil type. Cytotoxic studies showed that they demonstrate moderate activity against human cell lines HL-60 (promyelocytic leukemia) and A-549 (lung carcinoma) [20].

It is assumed that even the known antibiotics of psychrophilic strains may differ in their structure from those synthesized by mesophilic microorganisms, which may be an important aspect in the fight against forms of pathogenic and opportunistic human microorganisms that are resistant to the antibiotics used in medical practice [21].

The goal of this work was to evaluate the antibiotic activity of a collection of psychrophilic micromycetes isolated from various soils of the Arctic and Antarctic and the bottom soils of Lake Baikal, as well as the effect of temperature on the metabolic activity and biosynthesis of antibiotics.

**MATERIALS AND METHODS**

We used 98 strains of psychrophilic and psychrotolerant micromycetes from the collection of fungi cultures from extreme habitats of the Moscow State University, 21 of which were isolated from the soils of Antarctica [22–25] and 77 were taken from the soils (depth 5–250 m) of Lake Baikal [26].

To determine the species attribution of strains, preliminary identification was carried out according to cultural and morphological characteristics. The DNA was isolated from pure micromycete cultures according to the procedure by Glushakova et al. [27]: the biomass of a 5- to 6-day-old culture was transferred into 2-mL Eppendorf tubes; 400 μL of glass beads (300–500 μm in diameter) and 500 μL of lysis buffer, 50 mM TrisBase, 250 mM NaCl, 50 mM EDTA, 0.3% SDS, pH 8.0, were added. The prepared mixture was vortexed at a speed of 3500 rpm for 15 min, incubated for 1 h at 65°C, then vortexed again for 15 min, and centrifuged at 13400 g for 10 min. The supernatant was then collected.

To amplify the rDNA region containing the D1/D2 domain of the 26S rDNA region, the primers ITS1f (5' CTTGGTCAATTAGAAGGTA) and NL4 (5' GGTCGTGTTCAGAAGCC) and ScreenMix PCR mixtures (Evrogen, Moscow) were used.

The thermocycler was used according to the following program: initial denaturation for 2 min at 96°C; 35 cycles of denaturation for 20 s at 96°C, primer annealing for 50 s at 52°C, DNA synthesis for 1.5 min at 72°C, final completion for 7 min at 72°C. The PCR product was purified with the BigDye XTerminator Purification Kit (Applied Biosystems, United States). The NL4 primer was used for sequencing.

The DNA sequencing was performed with the BigDye Terminator V3.1 Cycle Sequencing Kit (Applied Biosystems, United States) with subsequent analysis of the reaction products on an Applied Biosystems 3130xl Genetic Analyzer at Syntol Research and Production Company (Moscow). The obtained chromatograms were identified based on data from the NCBI Genbank (http://blast.ncbi.nlm.nih.gov/) and the CABI Bioscience Database Index Fungorum (http://www.indexfungorum.org).

The ability to synthesize antimicrobial compounds was evaluated with the block method [28]. For further studies, strains that showed the maximum antibiotic activity were selected and then cultivated in liquid media. Czapek and Saburo standard nutrient media were used. Micromycetes were grown with the stationary method in 750-mL Erlenmeyer flasks for 14 days or with the submerged method on an Innova 40R shaker-incubator (Eppendorf New Brunswick, United States). The culture liquid (CL) was separated via filtration through membrane filters on a Seitz funnel under vacuum. Then CL was extracted three times with ethyl acetate or butanol in a ratio of 5:1. The obtained extracts were evaporated in a vacuum on a Rotavapor–RBüchi rotary evaporator (Switzerland) at 42°C to dryness; the residue was dissolved in aqueous 50% ethanol, and alcoholic concentrates were obtained. The antimicrobial activity was determined in the original CL, in the alcoholic extracts of CL, and in the mycelium extracts with sterile paper disks (St. Petersburg Pasteur Institute, Russia) soaked in extracts and dried under sterile conditions. Standard disks with fluconazole for fungi (40 μg, St. Petersburg Pasteur Institute, Russia) and amoxicillin/clavulonic acid for bacteria (20/10 μg, St. Petersburg Pasteur Institute, Russia) were used as controls. The following test strains were used to assess the fungicidal activity: mold fungus *Aspergillus niger* INA 00760 and yeast *Candida albicans* ATCC 2091.

The antibacterial activity was assessed with the following test strains: gram-negative bacterium *Escherichia coli* ATCC 25922; gram-positive bacterium *Bacillus subtilis* ATCC 6633; gram-positive bacteria *Staphylococcus aureus* 209P and *Micrococcus luteus* NCTC 8340; and pectobacteria *P. carotovorum* and *P. savastanoi*.

The test culture of *B. subtilis* ATCC 6633 was grown on the Gause medium no. 2 with the following
composition (g/L): 2.5 tryptone (or 30 mL Hottinger broth), 5 peptone, 5 sodium chloride, 10 glucose. S. aureus 209P and M. luteus NCTC 8340 were grown on meat peptone agar (MPA) medium (Research Center for Pharmacotherapy, Russia), and E. coli ATCC 25922 was grown on lysogen-broth LB medium (tryptone soy agar). Cultures of the micromycetes A. niger INA 00760 and C. albicans ATCC 2091 were grown on Czapek medium. The cultures were preliminarily grown in test tubes with nutrient agar slant, after which their cells were suspended in saline to a turbidity of 0.5 according to the McFarland standard (1.5 × 10⁸ CFU/mL) and were used within 15 min. One-day cultures of bacteria and 5-day cultures of fungi and yeasts were used. All test cultures were obtained from the culture collection of the Research Institute of New Antibiotics.

The cultural liquid extracts of the most promising strains of psychrotolerant micromycetes as producers were analyzed and separated into active fractions via analytical reversed-phase high-performance liquid chromatography (RP-HPLC) [29] with an XBridge 5 μm 130 Ang analytical column 250 × 4.6 mm (Waters, Ireland) in a linear gradient of increasing concentration of acetonitrile as a mobile phase (elucent A, 0.1% trifluoroacetic acid, TFA, in MQ deionized water; eluent B, 80% acetonitrile with 0.1% aqueous TFA) at a flow rate of 950 μL/min. Ultrgradiant acetonitrile from Panreac (Spain) and TFA from Sigma-Aldrich (United States) were used for RP-HPLC. The separated substances were detected at a wavelength of 214 nm in a concentration gradient of eluent B: 16–28% in 12 min; 28–55% in 20 min; 55–85% in 30 min, and 85–95% in 5 min, followed by isocratic elution for 10 min.

To obtain fractions in amounts sufficient for subsequent structural and functional analysis, 300 μL of the concentrate was applied once to an XBridge BEH 130 Ang 4.6 × 250 mm 5 μm analytical column for reversed-phase HPLC (Waters, Ireland) at a mobile phase flow rate of 1.1 mL/min. The linear gradient was 16–70% buffer B (80% acetonitrile in 0.1% TFA) in 50 min followed by 70–95% B in 5 min and isocratic elution for 15 min. The absorption detection was carried out at a wavelength of 220 nm.

Modification of the N-terminal amino group with Coumarin 343 X activated ester was carried out according to the following procedure [30].

Approximately 200 μg of the lyophilized substance was dissolved in 500 mM PBS NH₄HCO₃, pH 7.28 buffer, to a concentration of about 1 mg/mL. 1080 μL of a solution of Coumarin 343 XFITC activated ester (Sigma-Aldrich, United States) in 80% aqueous dimethylformamide (DMF) at a concentration of 4010 μg/mL was added to the resulting solution. It was thoroughly mixed and incubated for 1 h at room temperature 37°C in the dark. The reaction products were separated by analytical RP-HPLC on an XBridge BEH C18 4.6 × 250 mm column (Waters, Ireland) in a linear gradient of solvent B (80% CH₃CN, 0.1% TFA) from 16 to 28% for 12 min; (basic) and 28–55% in 10 min; 55–85% in 20 min (additional) at a flow rate of 0.935 mL/min. Absorption was detected at wavelengths of 214 and 437 nm.

The molecular weights of the active peaks of compounds were determined via ultra high performance liquid chromatography/mass spectrometry (UHPLC-MS) with a Thermo Finnigan LCQ Deca XP Plus ion trap mass spectrometry setup (ThermoFisher Scientific, United States) and a Thermo Accela UPLC high pressure chromatograph (ThermoFisher Scientific, United States) equipped with a YMC Triart microcolumn (C₁₈ 150 × 2 mm, 1.9 μm) (YMC Co., Japan) [31]. The signal was detected by the total ion current during electrospray ionization (ESI(+), 150–2000 a.u.). The samples were dissolved in a mixture of water/methanol/acetic acid (88 : 10 : 2) to a final concentration of about 1 mg/mL.

The absorption spectra of active compounds in the range of 200–600 nm were recorded by a UV-1800 spectrophotometer (Shimadzu, Japan) with 2-mL quartz cuvettes with an optical path length of 1 cm.

RESULTS AND DISCUSSION

The evaluation of the antimicrobial activity of 77 strains from the bottom soils of Lake Baikal against micromycetes and bacteria showed that the cultures are mainly characterized by their antibacterial activity. Thus, the proportion of cultures with antymycotic activity against A. niger INA 00760 was 2.6%, while those with antibacterial activity against B. subtilis ATCC 6633 made up 31.1% of the total number of studied strains (Table 1). Representatives of Trichoderma, Penicillium, Coniochaeta, and Daldinia genera showed the highest antibacterial activity, and representatives of micromycetes of the Trichoderma genus showed the highest antymycotic activity. It is important to note that, in this case, representatives of micromycetes of Trichoderma and Penicillium genera were found more often than others among the isolated isolates [32, 33].

The evaluation of the antimicrobial activity of 21 Antarctic soil isolates in relation to the test strains revealed relatively few cultures, namely, 4.8%, that showed high antibacterial activity and belonged to representatives of the Penicillium genus. It should be noted that none of the tested isolates had high antymycotic activity.

Thus, based on our results, the antibacterial activity predominates among the psychrotolerant strains. This specificity can be explained by the fact that the bacterial community of these soils is represented by much greater species diversity as compared with micromycetes. Thus, the production of antibiotics seems to be an effective method of interspecies com-
temperature changes occurring on different time scales (from daily to seasonal and longer periods) can have an important impact on the survival and evolution of microorganisms. In polar soils, antibiotic activity was demonstrated at temperatures up to 15°C [34]. The strain Penicillium vulpinum KPB F-290 exhibited high antimicrobial activity against opportunistic strains and B. subtilis ATCC 6633. The zones of inhibited growth of these test cultures reached 15 ± 2 mm and 31 ± 2 mm, respectively. Also, the strain was active against the phytopathogenic pectobacteria P. carotovorum and P. savastanoi, which cause soft rot in potatoes, and showed insignificant antimicrobial activity during both stationary cultivation and submerged cultivation against St. aureus 209P and M. luteus NCTC 8340. Various cultivation methods were tested in order to increase the biosynthesis of the antibiotic complex: stationary and submerged cultivation with a shaker-incubator (Table 3). For the maximum production of antibiotic substances by the strain, the optimal cultivation method is stationary, and ethyl acetate is the best extractant from the culture liquid.

Further, a scheme for the separation of the antibiotic complex of ethyl acetate and butanol extracts of the culture liquid of the strain Penicillium vulpinum KPB F-290 after stationary cultivation via analytical RP-HPLC was developed. This resulted in the obtainment of about 40 separate fractions (Fig. 1). The production of components of the strain Penicillium vulpinum KPB F-290 was scaled at an optimal load on the total substance and under the conditions of an optimized gradient.

In the ethyl acetate extract, the highest antimicrobial activity was typical for four fractions (290E-32, 290E-36, 290E-37, and 290E-39), which were eluted from the column in the range of 41–47 min (Fig. 1a). At the same time, the presence of inhibitory properties of the total fraction that did not bind to the stationary phase (downfall) (290E-1) was separately checked. Fractions 290E-1 and 290E-39 inhibited growth of B. subtilis ATCC 6633 and Candida albicans ATCC 2091; the size of the inhibition zones varied within 30/17 ± 0.1 and 29/23 ± 0.2 mm, respectively. Fractions 290E-32, 290E-36, and 290E-37 had the antifungal activity against A. niger INA 00760; the size of

Table 1. Total number of cultures (%) showing activity against B. subtilis ATCC 6633 and A. niger INA 00760 test strains

| Ecosystem   | Cultures Total | Inactive | Weakly active | Moderately active | Highly active |
|-------------|----------------|----------|---------------|-------------------|---------------|
| Lake Baikal | 77             | 13 (16.9%) | 57 (74%)      | 35 (45.5%)        | 12 (15.6%)    |
|             |                |          | 5 (6.5%)      | 6 (7.8%)          | 24 (31.1%)    | 2 (2.6%)     |
| Antarctica  | 21             | 7 (33.3%) | 12 (57.1%)    | 8 (38.1%)         | 5 (23.8%)     | 1 (4.8%)     | 0            |

The growth inhibition zone of test strains by inactive strains is 0 mm; weakly active, 1–15 mm; moderately active, 16–20 mm; highly active, 21 mm or more.
Table 2. Antimicrobial activity of selected strains at different temperatures*

| Isolates                              | Test organisms | Growth inhibition zones (mm) at different cultivation temperatures |
|---------------------------------------|----------------|---------------------------------------------------------------------|
|                                       |                | 15°C                   | 20°C                   |
| **Cadophora luteo-olivacea MT303851** | *B. subtilis ATCC 6633* | 7 ± 0.3                | 18 ± 0.3               |
|                                       | *E. coli ATCC 25922* | 0                      | 0                      |
|                                       | *A. niger INA 00760* | 6 ± 0.1                | 10 ± 0.1               |
|                                       | *C. albicans ATCC 2091* | 6 ± 0.2                | 10 ± 0.2               |
| **Acremonium zonatum MT303852**       | *B. subtilis ATCC 6633* | 8 ± 0.2                | 10 ± 0.6               |
|                                       | *E. coli ATCC 25922* | 0                      | 0                      |
|                                       | *A. niger INA 00760* | 6 ± 0.1                | 9 ± 0.2                |
|                                       | *C. albicans ATCC 2091* | 8 ± 0.4                | 17 ± 0.3               |
| **Cladosporium cladosporioides KPB F-288** | *B. subtilis ATCC 6633* | 0                      | 0                      |
|                                       | *E. coli ATCC 25922* | 6 ± 0.3                | 10 ± 0.2               |
|                                       | *A. niger INA 00760* | 0                      | 0                      |
|                                       | *C. albicans ATCC 2091* | 0                      | 0                      |
| **Penicillium vulpinum KPB F-290**    | *B. subtilis ATCC 6633* | 10 ± 0.5               | 31 ± 0.4               |
|                                       | *E. coli ATCC 25922* | 9 ± 0.4                | 25 ± 0.1               |
|                                       | *A. niger INA 00760* | 8 ± 0.1                | 15 ± 0.1               |
|                                       | *C. albicans ATCC 2091* | 9 ± 0.3                | 22 ± 0.3               |
| **Antarctomyces psychrotrophicus MT303855** | *B. subtilis ATCC 6633* | 0                      | 0                      |
|                                       | *E. coli ATCC 25922* | 0                      | 0                      |
|                                       | *A. niger INA 00760* | 0                      | 0                      |
|                                       | *C. albicans ATCC 2091* | 7 ± 0.1                | 10 ± 0.6               |
| **Sarocladium kiliense KPB F-292**    | *B. subtilis ATCC 6633* | 6 ± 0.1                | 10 ± 0.2               |
|                                       | *E. coli ATCC 25922* | 0                      | 0                      |
|                                       | *A. niger INA 00760* | 0                      | 0                      |
|                                       | *C. albicans ATCC 2091* | 0                      | 0                      |

* Extracts from CL of cultures grown at 4 and 10°C did not inhibit growth of test strains; no growth inhibition zones were observed.

Table 3. Growth inhibition zones of test cultures by *P. vulpinum* KPB F-290 strain during stationary and submerged cultivation

| Method of *P. vulpinum* KPB F-290 cultivation | Growth inhibition zones of test cultures by ethyl acetate/butanol extracts (10 mg/disk), mm |
|-----------------------------------------------|------------------------------------------------------------------------------------------|
|                                               | *B. subtilis ATCC 6633* | *E. coli ATCC 25922* | *A. niger INA 00760* | *C. albicans ATCC 2091* |
| Stationary                                    | 31/25                                                                                     | 15/19 | 11/0 | 14/13 |
| Submerged                                     | 18/19                                                                                     | 11/11 | 0/0  | 12c/12 |

their growth inhibition zones was within 15/22/27 ± 0.2 mm, respectively. Fraction 1 was characterized by relatively polar properties and was assigned to the β-lactam antibiotics (in particular, those of the penicillin series), while four other compounds had more pronounced hydrophobic properties. The highest antimicrobial activity was also noted for hydrophobic fractions 290B-25, 290B-26, and 290B-29 of the butanol extract, which also eluted in the same time range as the active components of 290E (Fig. 1b). All individual compounds had antifungal activity against *A. niger* INA 00760 and *C. albicans*.
ATCC 2091, while fraction 290B-26 also had antibacterial activity against *E. coli* ATCC 25922, and fraction 290B-29 had antibacterial activity against *B. subtilis* ATCC 6633. It should be noted that ethyl acetate turned out to be more effective for *P. vulpinum* CL compounds than butanol: the total solute yield was significantly higher during qualitative assessment (Fig. 1). As for the retention zone of the group of active components, it is worth noting their partial coincidence in terms of the presence in each of the extracts. Thus, fraction 290E-39 corresponded to 290B-29 in terms of the retention time on the column, which is confirmed by the spectrum of their antimicrobial properties.

For fungi, the minimum inhibitory concentration (MIC) of fractions against *A. niger* INA 00760 ranged from 6.25 to 12.5 μg/mL. The MIC against *C. albicans* ATCC 2091 ranged from 3.125 to 6.25 μL/mL. For bacteria, the MIC against *B. subtilis* ATCC 6633 was 25 μg/mL, and it was about 100 μg/mL against *E. coli* ATCC 25922.

For further structural characterization, fraction 290E-39 (290B-29) was chosen due to its highest yield as compared with the rest of fractions. Thus, as a result of its analysis with the ESI-MS method, the total mass spectrum with a number of predominant *m/z* signals in [M + H] mode (756.57, 782.57, 844.69, and 885.55 Da) was obtained, as well as some minor ones (718.54 and 744.56 Da). The presence of a characteristic isotopic distribution was shown for each of the detected *m/z* values; there were no differences in masses between the respective *m/z* values, which corresponded to a standard modification (e.g., methyl or hydroxyl groups). Therefore, the obtained values may correspond to the fragmentation spectrum of the metabolite with a [M + H] mass of 844.69 Da with a probable [M + H] derivative of 885.55 Da (Fig. 2).
In order to identify the presence of free amino groups in the studied molecule, which, in particular, could indicate its possible peptide nature, the modification reaction of the native compound 290E-39 (290B-29) with an organic fluorophore, Coumarin 343 X activated ester, was carried out, followed by the detection of reaction products via analytical RP-HPLC. The nature of the change in the chromatographic mobility of the detected peaks allows a conclusion on at least one derivative (data not shown). In addition, the absorption spectrum of the studied compound showed a profile close to that typical for most gene-encoded polypeptides with characteristic values of absorption minima and maxima, respectively, at wavelengths less than 230 nm and in the range of 260–280 nm (Fig. 3).

Thus, as a result of the study, the psychotolerant strain \textit{P. vulpinum} KPB F-290 was selected, and the complex of its secondary metabolites with the antimicrobial activity was studied. One compound can be classified as a \(\beta\)-lactam antibiotic (in particular, of the penicillin series); in addition, a new, active polypeptide with an antimicrobial effect against gram-positive bacteria, including phytopathogenic pectobacteria, was isolated.

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**COMPLIANCE WITH ETHICAL STANDARDS**

The authors declare that they have no conflicts of interest. This article does not contain any studies involving animals or human participants performed by any of the authors.

**REFERENCES**

1. Bull, A.T., in \textit{Extremophiles Handbook}, Horikoshi, K., Ed., Tokyo: Springer, 2011, pp. 1204–1240. https://doi.org/10.1007/978-4-431-53898-1
2. Bull, A.T. and Googfellow, M., \textit{Microbiology}, 2019, vol. 165, no. 12, pp. 1252–1264. https://doi.org/10.1099/mic.0.00822
3. Bull, A.T., in \textit{Extremophiles Handbook}, Horikoshi, K., Ed., Tokyo: Springer, 2011, pp. 3–15. https://doi.org/10.1007/978-4-431-53898-1
4. De Maayer, P., Anderson, D., Cary, C., and Cowan, D.A., \textit{EMBO Rep.}, vol. 15, no. 5, pp. 508–517. https://doi.org/10.1002/embr.201338170
5. Schmitt, E.K., Hoepfner, D., and Krastel, P., \textit{J. Ind. Microbiol. Biotechnol.}, 2016, vol. 43, no. 2, pp. 249–260.
6. Butler, M.S., Blaskovich, M.A., and Cooper, M.A., \textit{J. Antibiott.}, 2017, vol. 70, no. 1, pp. 3–24.
7. Imhoff, J.F., \textit{Mar. Drugs}, 2016, vol. 14, no. 1, pp. 19–37.
8. Arenz, B.E., Held, B.W., Jurgens, J.A., Farrell, R.L., and Blanchette, R.A., \textit{Soil Biol. Biochem.}, 2006, vol. 38. https://doi.org/10.1016/j.soilbio.2006.01.016
9. Shevchenko, M., Sukhikh, S., Babich, O., Noskova, S., Ivanova, S., Lisun, V., et al., \textit{Microorganisms}, 2021, vol. 9, no. 1521, pp. 1–12. https://doi.org/10.3390/microorganisms9071521
10. Madronich, S., McKenzie, R.L., Bjorn, L.O., and Caldwell, M.M., \textit{J. Photochem. Photobiol.}, 1998, vol. 46, pp. 5–19.
11. Montiel, P.O., \textit{Cryo. Lett.}, 2000, vol. 21, pp. 83–90.
12. Li, Y., Wadso, L., and Larsson, L., \textit{J. Appl. Microbiol.}, 2009, vol. 106, pp. 1494–1501. https://doi.org/10.1111/j.1365-2672.2008.04110.x
13. O’Brien, K., Leichenko, R., Kelkar, U., Venema, H., Aandahl, G., Tompkins, H., et al., \textit{Glob. Environ. Change}, 2004, vol. 14, pp. 303–313. https://doi.org/10.1016/j.gloenvcha.2004.01.001
14. Figueroa, L., Jiménez, C., Rodriguez, J., and Areche, C., \textit{J. Nat. Prod.}, 2015, vol. 78, pp. 919–923.
15. Frisvad, J.C., Frank, J.M., Houbraken, J.A.M.P., Kuijpers, A.F.A., and Samson, R.A., \textit{Stud. Mycol.}, 2004, vol. 50, pp. 23–43.

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16. Niu, S., Liu, D., Hu, X., Proksch, P., Shao, Z., and Lin, W., *J. Nat. Prod.*, 2014, vol. 77, pp. 1021–1030. https://doi.org/10.1021/np5000457

17. Svahn, K.S., Chryssanthou, E., Olsen, B., Bohlin, L., and Goransson, U., *Fungal Biol. Biotechnol.*, 2015, vol. 2, no. 1, pp. 1–8. https://doi.org/10.1186/s40694-014-0011-x

18. Vaca, I. and Chavez, R., in *Fungi of Antarctica*, Cham: Springer, 2019, pp. 265–283. https://doi.org/10.1007/978-3-030-18367-7_12

19. Ibrar, M., Ullah, M.W., Manan, S., Farooq, U., Rafiq, M., and Hasan, F., *Appl. Microbiol. Biotechnol.*, 2020, pp. 1–25. https://doi.org/10.1007/s00253-020-10399-0

20. Lin, A., Wu, G., Gu, Q., Z.T, and Li, D., *Arch. Pharm. Res.*, 2014, vol. 37, no. 7, pp. 839–844.

21. Sánchez, L.A., Gómez, F.F., and Delgado, O.D., *Extremophiles*, 2008, vol. 13, pp. 111–120.

22. Lysak, L.V., Maksimova, I.A., Nikitin, D.A., Ivanova, A.E., Kudinova, A.G., and Soina, V.S., *Vestn. Mosk. Univ.*, 2018, vol. 73, no. 3, pp. 132–140. https://doi.org/10.1134/S0026364818100059

23. Nikitin, D.A., *Mikol. Fitopatol.*, 2021, vol. 55, no. 2, pp. 79–104. https://doi.org/10.31857/S0026364821020070

24. Nikitin, D.A., Marfenina, O.E., Kudinova, A.G., Lysak, L.V., Megelov, N.S., Dolgikh, A.V., et al., *Eurasian Soil Sci.*, 2017, vol. 50, no. 9, pp. 1086–1097. https://doi.org/10.1134/S1064229317070079

25. Nikitin, D.A. and Semenov, M.V., *Microbiology* (Moscow), 2022, vol. 91, no. 1, pp. 1–13.

26. Sykhikh, S.A., Babich, O.O., Dyshlyuk, L.S., and Bulgakova, O.M., Characteristics of microbial communities of Lake Baikal, in *International Scientific Review of the Problems of Natural Sciences and Medicine. Collection of Scientific Articles X International Correspondence Scientific Specialized Conference*, USA, Boston, 2019, pp. 49–55.

27. Glushakova, A.M., Kachalkin, A.V., and Chernov, I.Y., *Eurasian Soil Sci.*, 2011, vol. 44, no. 8, pp. 886–892. https://doi.org/10.1134/S1064229311080059

28. Egorov, N.S., *Osnovy ucheniya ob antibiotikakh* (Fundamentals of the Doctrine of Antibiotics), Moscow: Mosk. Gos. Univ., Nauka, 2004, 6th ed.

29. Tan, Z.T., Leow, H.Y., Lee, D.C.W., Karisnan, K., Song, A.A.L., Mai, C.W., et al., *Open Biotechnol. J.*, 2019, vol. 13, pp. 18–26. https://doi.org/10.2174/1874070701913010018

30. Zheng, L., Zhao, H., Han, Y., Qian, H., Vukovic, L., Mecinovic, J., et al., *Nat. Chem.*, 2019, vol. 11, no. 4, pp. 359–366. https://doi.org/10.1038/s41557-018-0204-7

31. Efimenko, T.A., Glukhova, A.A., Demiankova, M.V., Boykova, Y.V., Malkina, N.D., Sumarukova, I.G., et al., *Life* (Basel), 2020, vol. 10, no. 91, pp. 1–16. https://doi.org/10.3390/life10060091

32. Nikitin, D.A., Lysak, L.V., Kutovaya, O.V., and Gracheva, T.A., *Eurasian Soil Sci.*, 2021, vol. 54, no. 11, pp. 1689–1704. https://doi.org/10.1134/S1064229321110107

33. Nikitin, D.A., Semenov, M.V., Semikolennykh, A.A., Maksimova, I.A., Kachalkin, A.V., and Ivanova, A.E., *Mikol. Fitopatol.*, 2019, vol. 53, no. 4, pp. 210–222.

34. Bérdy, J., *J. Antibiott.*, 2005, vol. 58, no. 1, pp. 1–26. https://doi.org/10.1038/ja.2005.1

35. Bell, T.H., Callender, K.L., Whyte, L.G., and Greer, C.W., *Biolog*, 2013, vol. 2, no. 2, pp. 533–554. https://doi.org/10.3390/biology2020533

36. Convey, P., Chown, S.L., Clarke, A., Bokhorst, S., Cummings, V., et al., *Ecol. Monogr.*, 2014, vol. 84, pp. 203–244. https://doi.org/10.1890/12-2216.1

37. Davey, M., Pickup, J., and Block, W., *Antarct. Sci.*, 1992, vol. 4, pp. 383–388.

38. Peck, L.S., Convey, P., and Barnes, D.K.A., *Biol. Rev.*, 2006, vol. 81, pp. 75–109. https://doi.org/10.1017/S1464793105006871

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