Unexplored potential: Biologically active compounds produced by microorganisms from hard-to-reach environments and their applications

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Rapid development of antibiotic resistance of bacteria and fungi, as well as cancer drug resistance, has become a global medical problem. Therefore, alternative methods of treatment are considered. Studies of recent years have focused on finding new biologically active compounds that may be effective against drug-resistant cells. High biodiversity of hard-to-reach environments offers sources to search for novel molecules potentially applicable for medical purposes. In this review article, we summarize and discuss compounds produced by microorganisms from hot springs, glaciers, caves, underground lakes, marine ecosystems, and hydrothermal vents. Antibacterial, antiviral, antifungal, anticancer, anti-inflammatory, and antioxidant potential of these molecules are presented and discussed. We conclude that using compounds derived from microorganisms occurring in extreme environments might be considered in further studies on development of treatment procedures for diseases caused by drug-resistant cells.

Keywords: biologically active compounds, caves, hot springs, hydrothermal vents, underground lakes, glaciers, antimicrobial activity, anticancer activity, antioxidant activity

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Abbreviations: ADR, doxorubicin; ATTC, American Type Culture Collection; CD, circular dichroism; CPE, cytotoxic effect; DDM, disk diffusion method; DEEL-3, diethyl ether extract; EPS-2, extracellular polysaccharide; GC-MS, gas chromatography-mass spectrometry; MCI, mild cognitive impairment; MRSA, methicillin-resistant *Staphylococcus aureus*; MTT, 3-(4,5-dimethylthiazol-2-yl)-2,5 diphenyl tetrazolium bromide; NMR, nuclear magnetic resonance; PBMC, peripheral blood mononuclear cells; PNPP, *p*-nitrophenyl phosphate; PPG, purpuragallin; ROS, reactive oxygen species; UV, ultraviolet; VRE, vancomycin-resistant Enterobacter
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INTRODUCTION

Compounds with biological activities are widely used in medicine. However, its enormous development, which took place mainly in the last decade, and the wide use or even abuse of these compounds, led to disturbing phenomena such as antibiotic resistance of bacteria and fungi or drug resistance of cancer cells. Every year, in the United States, antibiotic-resistant bacteria and fungi cause as many as 2,868,700 infections, among which 35,900 are fatal. It is estimated that in the absence of measures to limit the spread of this type of strains, the number of deaths caused by them will increase sharply (Center for Disease Control and Prevention, 2019). In 2019, 9,297,000 people died from malignant tumors. Due to the large individuality of the cancerous tissues, it is even difficult to estimate how many of them were characterized by drug resistance. It is certain, however, that this phenomenon accompanies cancer more and more often, making effective treatment difficult (World Health Organization, 2020).

Antibiotic resistance occurs when microbes develop the ability to avoid death from antibiotics. According to a report by the Centers for Disease Control and Prevention, in the United States, the most urgent and alarming strains of antibiotic-resistant bacteria include (i) carbapenem-resistant *Acinetobacter*, (ii) *Candida auris*, (iii) *Clostridium difficile*, (iv) carbapenem-resistant *Enterobacteriaceae*, (v) *Neisseria gonorrhoeae* (Center for Disease Control and Prevention, 2019). Some of these microbes are resistant to only one class of antibiotics, such as *Acinetobacter*, but other, like *Neisseria gonorrhoeae*, are reveal resistance to almost all known antibiotics (Blair et al., 2015). Moreover, these Centers also draw attention to drug-resistant strains of *Shigella* or *Streptococcus pneumoniae*, as well as multi-drug resistant *Pseudomonas aeruginosa* (Center for Disease Control and Prevention, 2019). These bacteria acquire resistance to antibiotics through a number of molecular mechanisms that can be broadly categorized into 3 types: (i) minimizing intracellular antibiotic concentration, (ii) modifying the target of the antibiotic, and (iii) inactivating the antibiotic. Detailed mechanisms of bacterial resistance to antibiotics were described by Blair et al. (2015). Likewise, in the case of fungi, alarming antibiotic resistance due to diverse molecular mechanisms, such as overexpression of drug efflux pumps, mutations in the *ERG11* gene (encoding 14α-demethylase), reduction of enzyme levels for a drug, or changes in sterol biosynthesis efficiency is observed (Balkis et al., 2002).

Cancer treatment is a huge challenge in today’s medicine. The resistance of tumors to anti-cancer drugs, especially chemotherapy and molecularly targeted therapies, creates another problem, adding next building block to this already difficult situation. Tracheal, bronchial and lung cancers are the most lethal of all known tumors. In 2019, as many as 1,784,000 people died because of this (World Health Organization, 2020). In the case of the most common non-small cell lung cancer, small cell lung cancer or breast cancer, resistance to drugs used in conventional chemotherapy is increasingly observed.
(Shanker et al., 2010; Sawicka et al., 2018). Moreover, it is common for these tumors to be multi-drug resistant, meaning that they have acquired resistance to drugs with different mechanisms of action. As in the case of bacteria and fungi, there are many mechanisms that lead to cancer drug resistance, including (i) inactivation or reduction of drug activity, (ii) inhibition of cell death, (iii) increased efficiency of DNA repair systems, (iv) changes in the level or the molecular target structure of drugs, (v) increasing drug efflux, (vi) epigenetic changes (Holohan et al., 2013).

Due to the antibiotic resistance of microbes and the drug resistance of tumors, new forms of treatment of bacterial infections and neoplastic diseases should be introduced. One of the solutions to these problems may be the invention of new therapeutic approaches, and the other is the search for new compounds with biological activities that could be effective against microbes or cancer. The search for such compounds in hard-to-reach extreme environments could potentially be effective. Hitherto unknown environments may be characterized by a large variety of such molecules.

This review highlights extreme habitats such as thermal springs, volcanic waters, caves, underground lakes, marine ecosystems, hydrothermal vents and glaciers as a source of organisms that can produce new compounds with antimicrobial, antifungal, anticancer, and sometimes anti-inflammatory and antioxidant effects.

**COMPENDS PRODUCED BY MICROORGANISMS FROM HOT SPRINGS**

Hot springs, also called thermal springs, are springs with water temperature significantly higher than the surrounding air temperature. The majority of hot springs discharge groundwater which is warmed by shallow intrusions of magma in volcanic areas (Mahajan & Balachandran, 2017). Hot springs are inhabited by a group of heat-loving microbes called thermophiles, which thrive at high temperature. According to the optimal temperature of their growth, it is possible to divide them into three groups: moderate thermophiles (50–60°C), extreme thermophiles (60–80°C) and hyperthermophiles (over 80°C) (Kumar et al., 2019). Thermophiles show a diversity of molecular mechanisms which help them to resist to and correct the damage caused by high temperature. These comply (i) a high level of saturated fatty acids that creates an environment which helps to maintain the rigidity of cell wall; (ii) a high number of electrostatic and hydrophobic interactions; stabilizing bonds like disulfide bridges; (iii) the presence of a reverse DNA gyrase which brings positive supercoils in the thermophiles DNA that results in increasing the DNA melting point to the level required for optimum growth (Borgave et al., 2017). Thermophiles have drawn attention due to their unique features and the production of variable bioactive molecules and enzymes for biotechnological applications like industrial, agriculture and medical processes (Kumar et al., 2019; Benammar et al., 2020).

**Compounds with antibacterial activities**

In 2002, strains VK2 and VK21 of the *Bacillus* genus were collected and isolated from hot springs of the Kamchatka Peninsula. Analysis of 16S rRNA has shown that they most likely belong to the *Bacillus licheniformis* species. Filtered culture liquids of these strains have displayed lytic activity to the test strains of *Bacillus megaterium* VKM41, *Pseudomonas putida* I-97, *Staphylococcus* sp. SS1 and *Micrococcus luteus* E509 indicating their antibacterial activities. Subsequent study on antibiotic synthesis and properties has shown that they are peptides (Esikova et al., 2002). Similarly, antibacterial activity against *Bacillus pumilis* and *Bacillus subtilis* was found in methanolic extracts from seven species of cyanobacteria isolated from thermal springs of Geno. These species were *Oscillatoria subulata*, *O. tenus*, *O. limnetica*, *O. angusta*, *O. articulata*, *Synchocystis aquilata*, and *Synechococcus ceroides* (Heidari et al., 2012).

More detailed study on thermophilic bacteria collected from hot springs in Northern Tunisia led to isolation and identification of specific *Pseudomonas putida* strain. The cell-free supernatant of *P. putida* T01 strain showed antimicrobial activity against several Gram-negative and Gram-positive bacteria, including *Escherichia coli*, *Brevibacterium thermophila*, *Yersinia enterolitica*, *Hafnia* sp., *Salmonella enterica*, *Bacillus megaterium*, *Entrobacteriaca* and other *Pseudomonas* strains, which include food-borne pathogens. The results of that study proved that *P. putida* T01 produces a bacteriocin-like substance, putadicin T01 that may be useful in medicine and in a low processed preservation of food (Ghrairi et al., 2015).

Extensive research on isolation of antibacterial compounds from hot springs was carried out in 2016–2018. The study conducted by Alrumman and others (Alrumman et al., 2018) focused on investigation of thermophilic bacteria bioactivity collected from thermal springs in the Southern Saudi Arabia. Fifty out of 84 isolates have shown antibacterial effect against human pathogens, like *Candida albicans*, *Staphylococcus aureus*, *Proteus mirabilis*, *Klebsiella pneumonia* and *Shigella flexneri*. Four of these isolates were antagonistic against all of these pathogens. Genetic sequencing and phylogenetic analysis led to their identification as *Bacillus sorororius*, *Bacillus thermoporiferus*, *Brevibacillus borstelensis* and *Brevibacillus parabrevis*. Cell-free extracts GC-MS analysis of secondary metabolites detected 40 of them among which there were mephenisin, cyclohexyl acrylate, (3-aminopropyl) dibutyboranate (B. sorororius); etomidate, 1-methylp lactate, (3-aminopropyl) dibutyboran (B. borstelensis); tabtoxinine-β-lactame, nicotinyl alcohol (B. borstelensis); cyclohexyl acrylate, imiloxan (B. thermoporiferus). That study indicated that these isolates are a source of compounds that act against pathogenic microbes, including antibiotic resistant species like *Staphylococcus aureus* (Alrumman et al., 2019).

Tumbarski and others (Tumbarski et al., 2018) also looked for compounds against bacteria of the *Bacillus* genus. In the study performed on *Bacillus methylotrophicus* strain BM47 isolated from a thermal spring in Bulgaria, a peptide synthesized by this species was characterized as a bacteriocin. In vitro screening of *B. methylotrophicus* BM47 bacteriocin exhibited its activity against Gram-negative bacterium *P. aeruginosa*. However, this bacteriocin showed intensified activity against plant pathogenic fungi *Fusarium moniliforme*, *Aspergillus awamori*, *Penicillium* sp., *Aspergilus niger*. Thus, it is mostly considered as a biocontrol and plant protection agent (Tumbarski et al., 2018).

Furthermore, three different species of Actinobacteria (M1-1, M2-2, M3-3) were found in sediment samples collected from Ma’In thermal springs in Japan. 16S rRNA gene analysis showed that M1-1 isolate has 90% identity percentage with *Nocardiopsis sp.*, M2-2 is related in 97% with *Streptomyces* sp. and M3-3 is 99% related to *Nocardioides luteus*. Testing antibacterial activity by the agar well diffusion method exhibited M1-1 activity against *P. aeruginosa* ATCC 2785 and M2-2 activity against *S. aureus* ATCC 29213, *B. cereus* ATCC 11778, and *E. coli* ATCC. The M3-3 strain was active against *S. aureus* ATCC
Compounds produced by microorganisms from hard-to-reach environments

**Compounds produced by microorganisms from caves**

Caves are cavities, at least part of which is in constant darkness, with turbulent water flow and with eyeless, de-pigmented species present. There are different types of caves and different mechanisms of their formation, including (i) formed by mechanical process, like tectonic caves, (ii) formed by differential erosion and scour like sea caves, (iii) volcanic caves like lava tubes, (iv) glacial caves, like ice ore caves, and (v) solution caves, for example those formed by mixing freshwater with salt water (White et al., 2019). Caves are extreme habitats that have very specific conditions and environment. Caves can be sources of biological active compounds-producing organisms, mostly bacteria but also fungi and in one case even sponge. Such caves can be particularly rich in actinomycetes, but one can also find bacteria from various genera, including *Nonomuraea*, *Agrimonies*, *Nocardia*, *Rhodococcus*, *Micronosus* and *Bacillus* (Rangseekaew & Pathom-aree, 2019). Organisms can be found in different places of the cave, like cave soil (Jiang et al., 2015), rock wall (Yücel & Yamaç, 2010), moonmilk deposits (Adam et al., 2018), water and sediment (Klusaite et al., 2016).

Compounds with antibacterial and antifungal activities

Caves turned out to be an environment rich in bacteria that produce biologically active compounds. Isolates of many of these bacteria were tested against antibiotic-resistant bacterial strains, including those that cause severe infections in humans.

Cervamicin A, B, C, D isolated from bacteria, most closely related to *Streptomyces tendae* HKJ 0179, proved to be responsible for antibacterial activities against multidrug-resistant *Staphylococcus aureus* and vancomycin-resistant *Enterococcus faecalis* strains (Herold et al., 2003). Nakaew and others (Nakaew et al., 2009) also collected from cave in Thailand 377 Actinomycetes, most of which were nonstreptomycete. Eleven randomly selected isolates from nonstreptomycete isolates were tested against bacteria cells. Isolates PKN470 and PT708 showed activities against Gram-positive bacteria *Bacillus cereus*, methicillin-resistant *Staphylococcus aureus* (MRSA) and *Paenibacillus larvae* (Nakaew et al., 2009a; Nakaew et al., 2009b). Moreover, Turkish caves were tested for the activity of compounds isolated from them. Two hundred and ninety *Streptomyces* isolates were screened. One hundred and eighty of them were active against many strains of bacteria and fungi (*Pseudomonas aeruginosa* NRRL B-771, *Candida albicans* NRRL Y-12983, *Geotrichum candidum* NRRL Y-552, *Aspergillus flavus* NRRL 1957, *Aspergillus parasiticus* NRRL 465, *Bacillus cereus* ATCC 11778, *Staphylococcus aureus* ATCC 25923, *Escherichia coli* ATCC 25922, *Fusarium culmorum*, *Fusarium moniliforme*, MRSA, vancomycin-resistant *Enterobacter faciatus* (VRE), *Acinetobacter baumanii*). Interestingly, one of the isolates, belonging to *Streptomyces* sp. 1492, showed very strong antibacterial activity against VRE and MRSA (Yücel & Yamaç, 2010).

Five secondary metabolites (3 newly discovered and 2 previously known) with antibacterial activities were isolated from sponge *Xestospongia* sp. (Ankisetty & Slattery, 2012). Newly discovered metabolites were tested and showed antimicrobial activity against *Pseudomonas aeruginosa* and *Myobacterium intracelullare*. Moreover, undecyldigiosin isolated from *Streptomyces* sp. JS520, has antibacterial activities against *Micronosus lutens* and *Bacillus subtilis* (Stankovic et al., 2012). An antibacterial activity against *Bacillus cereus* TISTR 687, methicillin-resistant *Staphylococ-
cas aureus and Paenibacillus larvae LMG 9820T isolates from Actinomycete strain PT708T, classified as the Non-
omuoria genus, was collected from cave soil in Thailand (Nakaew et al., 2012). Then, Streptomycetes isolates from
Kotumsar cave (India) were tested against Escherichia coli MTCC 1667, Staphylococcus aureus MTCC 96, and Pse-
domonas aeruginosa JNM. A Streptomyces roeseri (KCA13) isolate showed a strong antibacterial activity against
E. coli and P. aeruginosa (Rajput et al., 2012).

Extensive research was also carried out by Tomova and others (Tomova et al., 2013) and Cheeptham and others
(Cheeptham et al., 2013). Bacteria isolated from the cave in Bulgaria belongs to four phyla, Proteobacteria (63%),
Actinobacteria (10.9%), Bacteroidetes (10.9%), and Firmicutes (6.5%). Antibacterial activity of the iso-
lates were tested against Bacillus subtilis ATCC 6533, Pseudomonas aeruginosa NBIMCC 1390, Xanthomonas or-
gena, and Rhodotorula mucilaginis 6526. Over 75% of the isolates demonstrated antimicrobial activity against these
strains (Tomova et al., 2013). Cheeptham and others (Cheeptham et al., 2013) collected 400 isolates from vol-
canic cave. Eight two of them were randomly selected to gene sequencing which revealed that almost 80% strains
belonged to the Streptomycetes genus and 6% belonged to Bacillus, Pseudomonas, Nocardia and Erwinia genera. Fifteen
percent of the sequences showed similarity to unidentified ribosomal RNA sequences in the library databases,
thus, more tests are needed to determine if they are newly discovered species. Screening of all 400 isolates showed that
some of them were active against extended spectrum ß-lactamase of Escherichia coli, MRSA, Actino-
bacter baumannii, Candida albicans, Pseudomonas aeruginosa, Mycobacterium smegmatis, Micrococcus luteus, and
Klebsiella pneumoniae (Cheeptham et al., 2013). Actinobacteria were also isolated from volcanic caves in Canada, the isolates
were screened for antibacterial activity. Twenty seven isolates showed such activity against at least one of the
tested bacteria, Proteus sp., Salmonella typhimurium, Staphylo-
coccus aureus, Escherichia coli, Pseudomonas aeruginosa, Listeria monocytyogenes, and Listeria innocua (Riquelme et al., 2017).

Compounds named hypogaeamicins B–D, isolated from Nonomuoria sp., and lipids extracted from two cy-
ano bacteria (Tocypus calypsos strain ATHU-CY 3314 and Phormidium melanochron CC8-201) were also tested
for antibacterial activities. Their extracts inhibited growth of Bacillus subtilis, Enterococcus faecalis, and Enterococ-
cus faecium (Derewacz et al., 2014). Compounds with anticancer activities

A cave in Georgia was a source of 874 cultures which were tested for their antibacterial activities on
Micrococcus luteus, Bacillus thuringiensis TL8, Escherichia coli BL21(DE3), and Pseudomonas sp. VR1. Fourteen percent
of these isolates had antibacterial activities, and 24 of them were exclusively active against Gram-positive bacte-
ria. For two very active strains (1350R2-TSA30-6 and 1410WF1-TSA30-2), chemical structures of the main compounds were determined and they were pyrrol-
yrazines pyrrol[1,2-alpyrazine-1,4-dione, hexahydro-
3-(2-methylpropyl) and pyrrol[1,2-alpyrazine -1,4-dione, hexahydro-
3-(phenylmethyl) (for 1350R2-TSA30-6 strain), and 1,2-benzendicarboxylic acid, bis(2-methyl-
propyl) ester (for 1410WF1-TSA30-2 strain) (Klusaite et al., 2016). Seventy eight isolates from genus Streptomyces
from moonmilk deposits were screened for their activities against microbes, Escherichia coli, Pseudomonas aeruginosa, Citrobacter freundii, Klebsiella pneumoniae, Bacil-

lus subtilis, Staphylococcus aureus, Micrococcus luteus, Candida albicans, Aspergillus fumigatus, Rasamonnia argillaceae, Penicil-
lium chrysogenum, and Trichophyton mentagrophytes. Ninety
four percent of isolates inhibited growth of Gram-
positive bacteria, Seventy one percent inhibited growth of Gram-negative bacteria, and Ninety four percent
inhibited growth of fungi. Moreover, 90% of the cave strains induced strong growth suppression against the
multi-drug resistant Rasamonnia argillacea (Maciejewski et al., 2016). Subsequent metagenomic study indicated that
40 isolates, collected from moonmilk deposits, are newly
discovered representatives of the genera Agromyces, Amycolatopsis, Kocuria, Micrococcus, Micromonospora, Nocar-
dia, Rhodococcus, and Streptomyces. Antibacterial activities of these isolates were tested using Gram-positive
and Gram-negative bacteria, including Escherichia coli, Pseu-
domonas aeruginosa, Citrobacter freundii, Klebsiella pneumoniae, Bacillus subtilis, Staphylococcus aureus, and Micrococcus luteus.

As many as 87% and 59% of the tested strains were active against Gram-positive and Gram-negative bacte-
ria, respectively (Adam et al., 2018). Then, 47 strains of bacteria (Streptomyces spp.) and 23 strains of fungi
(Penicillium spp.) were isolated from a cave in Algeria, and their antimicrobial activities were tested on various
bacterial and fungal strains. Most of Actinomycetes and Penicillium spp. were effective against S. aureus, M. luteus,
B. subtilis, L. monocytogenes, E. coli, K. pneumoniae, and C. albicans (Belyagoubi et al., 2018).

Recent studies were conducted by Ambrozić and others
(Ambrožič et al., 2019) and Paun and others (Paun et al., 2021). Seventy eight isolates from microbial mats
have been tested for antibacterial activities on different bacte-
ria. Between 10 and 25% of isolates were active against B. subtilis, MRSA, S. pseudointermedius, E. coli, and Salmonella enterica (Ambrožić Avguštin et al., 2019). Paun and others (Paun et al., 2021) performed studies
on isolates from 13,000-year old cave ice core. All isolates showed activity against Staphylococcus aureus and
Pseudomonas aeruginosa. Some of them inhibited growth of Enterobacter cloacae, E. cloacae, Pseudomonas aeruginosa, Es-
cherichia coli, clinical Klebsiella strains CK1, CK2, and CK3, and three Enterococcus faecium strains (19040 E1, E2, E3)
(Paun et al., 2021).
human prostate cancer (PC-3). The highest cytotoxicity was observed for the first three cell lines listed (Jiang et al., 2015). Moreover, huanglongmycin A showed a moderate cytotoxicity against human lung cancer and weak against ovarian cancer (SKOV3), cervical cancer (HeLa), and colorectal adenocarcinoma (Caco-2). Huanglongmycin B and C did not show cytotoxicity against tested cancer cell lines (Jiang et al., 2018).

**Compounds with anti-inflammatory and antioxidative activities**

Some of the compounds isolated from the caves are also characterized by their anti-inflammatory and antioxidative properties. It was observed that xenoclovin B, isolated from *Streptomyces* CB09001, has a strong anti-inflammatory effect. Tests conducted on murine macrophage RAW264.7 cell line showed that it can inhibit about 70% of NOX gene expression when applied at 20 μM (Jiang et al., 2019). Furthermore, undecylenoprodigiosin isolated from *Streptomyces* sp. JS520 expressed anti-inflammatory activities in terms of inhibiting autooxidation of linoleic acid (Stankovic et al., 2012).

**COMPONDS PRODUCED BY MICROORGANISMS FROM UNDERGROUND LAKES, MARINE ECOSYSTEMS AND HYDROTHERMAL VENTS**

Microorganisms living in extreme aquatic environments, such as underground lakes, hydrothermal vents, and marine polar regions, represent a promising arsenal of natural products that could represent the future of the pharmacology and biotechnology industry.

**Compounds with antibacterial and antifungal activities**

A novel antibiotic called cadoxamycin, belonging to the benzoxazole class, was obtained from an Atlantic Ocean deep-sea sediment, at a depth of 3,814 m. This compound was isolated from the *Streptomyces* sp. strain NTK 937. The structure of this compound was investigated by using mass spectrometry, NMR, and X-ray analysis. Its antimicrobial properties were shown against the Gram-positive bacteria *Bacillus subtilis* and *Staphylococcus luteus*, and the yeast *Candida glabrata* (Hohmann et al., 2009; Sivalingam et al., 2019).

Antibacterial and antifungal properties were found in 42 actinobacterial strains (40 were identified as the genus *Streptomyces*, and two belongs to the genera *Micromonospora* and *Pseudonocardia*) isolated from the endemic deepwater amphipods of Lake Baikal, belonging to *Ommatogammarus alternans* and *Ommatogammarus flavus*. Disk diffusion method (DDM) was used to examine the antimicrobial activities of obtained metabolites against seven model strains of microorganism, among others *Bacillus subtilis* ATCC 6633 or *Staphylococcus carnosus* ATCC 51365. It was found that over 70% of strains isolated from amphipods have antibacterial activity (Protasov et al., 2017).

In 2018, researchers isolated interesting actinobacteria that belong to *Streptomyces*, *Nocardia*, and *Nocardiopsis* genera. They derived from water surface of underground lakes from Badzheyskaya and Okhotnichya caves in Siberia. Antibiotic activity of the extracted metabolites was tested by using disk diffusion method (DDM) against several bacterial and fungal cultures types, among other *Escherichia coli* ATCC25922 or *Candida albicans* DSM1665. Ten out of 17 strains showed antibiotic activity against at least one tested bacterial or fungal culture (Voityekbovskaia et al., 2018).

The synthesis of silver nanoparticles (AgNPs) by the Gram-negative *Pseudomonas* strain, isolated from the Antarctic marine ciliate *Euplotes foucardii*, and showing antimicrobial activities against *Escherichia coli*, *Staphylococcus aureus*, and *Candida albicans* was reported (John et al., 2020). Silver nanoparticles were obtained by incubation of *Pseudomonas* cultures with silver nitrate (AgNO₃), and after that antimicrobial activity was tested against 12 human pathogens by using disk diffusion method (DDM) giving promising results (John et al., 2020; Giordano, 2020).

**Compounds with antiviral properties**

Marine-derived microorganisms can produce active compounds with antiviral activity, one of these is rubrolide S, obtained from the fungus *Aspergillus terraeus* OUCMDZ-1925, found in *Chelon haematoboeiulus* grown in the Yellow River Delta. Rubrolide S showed anti-influenza A (H1N1) virus activity with an IC50 value of 87.1 μM. The antiviral activity against H1N1 virus were tested by using viral cytopathic effect (CPE) inhibition assays (Zhu et al., 2014).

It was observed that cladosin C, a hybrid polypeptide, isolated from sediments collected in the Pacific Ocean from the *Cladocidium sphaeroporum* 2005-01-E3 strain, has mild anti-influenza A H1N1 virus activity with IC50 value of 276 μM (Wu et al., 2014).

Marine habitats offer an enormous sources of potential anti-HIV compounds. An example is 2-benzylpyrдин-4-one-containing metabolites, aspernnigrin C and malformin C, derived from *Aspergillus niger* SCSIO Jcsw6F30 which was isolated from the marine algae *Sargassum* sp., collected in Yongxing Island, South China Sea. This molecule exhibited moderate inhibitory activity against two viruses, H3N2 and EV71, with IC50 values of 17.0 and 9.4 mM, respectively (Fang et al., 2014).

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Interestingly clinical trials are reported with the compound named Plitidepsin (Aplidin®), isolated from the ascidian *Aplidium albicans*, in patients infected with SARS-CoV-2 (PharmaMar, 2020).

**Compounds with anticancer activities**

Cytotoxic activities of eremophila-type sesquiterpenes, isolated from the Antarctic deepsea fungal *Penicillium* sp. PR19 N-1, were determined by extensive NMR and mass spectroscopic analyses. Extracted metabolites showed potent inhibitory activity against A-549 cancer cells which were evaluated by using an SRB method and to HL-60 cell line using an MTT assay (Lan et al., 2014).

2-amino-6-hydroxy-[1,4]-benzoquinone, and its two derivatives, were isolated from deep-sea hydrothermal vents in the Eastern Pacific. These compounds are produced in *Geobacillus* sp. E263 infected with a thermophilic and lytic bacteriophage GVE2. Their structures were investigated by using gas chromatography/mass spectrometry (GC/MS) and Nuclear Magnetic Resonance (NMR), and then, cell proliferation was examined. The tested compounds showed a significant inhibition of the
proliferation of HGC-27 and MGC-803 (gastric cancer cells), MDA-MB-231 (breast cancer cells), and MDA-MB-435 (melanoma cells) cell lines. Strong cytotoxic activities against cancer cells have a potential to be candidates for anticancer drugs (Xu et al., 2017).

Butanolide A, a furanone derivative, and a sesquiterpene, guignarderemiphilane F, with six known compounds, were isolated from Antarctic marine fungus *Penicillium* sp. S-1-18. The structures of these compounds were investigated by using 1D- and 2D-NMR spectroscopic methods. Antitumor properties were tested for their protein tyrosine phosphatase 1B (PTP1B) inhibitory activity by using colorimetric assay, employing disodium p-nitrophenyl phosphate (PNPP). Butanolide A showed moderate activity against PTP1B with IC50 value of 27.4 μM (Zhou et al., 2018).

An antibacterial compound, 3-hydroxyquinclidic acid derivative, was isolated from *Streptomyces cyanogenicus* M-157, occurring in the deep sea at 1800 m depth in the central Cantabrian Sea. This compound showed cytoxic activity on HepG2 with an IC50 value of 51.5 μM (Ortiz-López et al., 2018; Sivalingam et al., 2019).

Li and others (Li et al., 2019) isolated three previously known discorhabdin alkaldoids, (−) − discorhabdin L, (+) − discorhabdin A, and (+) − discorhabdin Q, and three previously unknown discorhabdin analogs, (−) − 2-bromo-discorhabdin D, (−) − 1-acetyl-discorhabdin I, and (+) − 1-octacosatrenyl-discorhabdin I, extracted from a sponge *Latrunculia bijorae* from the Weddell Sea which is located off the Antarctic coast, showing potential anticancer activity. The structures of these metabolites were examined by extensive spectroscopy. Antitumor properties were tested on cell lines MDA-MB231 (human breast cancer line), A549 (lung carcinoma cell line), Hep G2 (liver cancer cell line), HT29 (colorectal adenocarcinoma cell line), A375 (malignant melanoma cell line), and HCT116 (colon cancer cell line). Moreover, the molecular modeling showed potential binding of discorhabdins to the anticancer targets involved in their anticancer activity (Li et al., 2019a).

Deinoxanthin is a compound from the carotenoid group, obtained from the bacteria *Deinococcus* sp. UDEC-P1 and *Arthrobacter* sp. UDEC-A13, isolated from the maritime areas of Patagonia and Antarctica. This compound showed antiproliferative activity of Neuro-2a (fast-growing mouse neuroblastoma cell line), Saos-2 (human osteosarcoma cell line), and MCF-7 (human breast cancer cell line) tumor cells (Tapia et al., 2019).

### Compounds with antioxidant properties

*Pseudomonas extremautralis*, isolated from a temporary water pond in Antarctica, is highly resistant to oxidative stress and temperature changes (Ayub et al., 2004). This property is due to the presence of high amounts of polyhydroxalkanoates (PHA), mainly occurring as polyhydroxybutyrate (PHB), a short chain length PHA (López et al., 2009). In addition, cold-induced down-regulation of the expression of genes encoding iron-related proteins may help to alleviate the oxidative stress, caused by iron, produced during the Fenton reaction (Tribelli et al., 2015).

Finally, genes coding for proteins involved in antioxidant activities, including superoxide dismutase, glutathione peroxidase, glutathione reductase, catalase, aconitase, thioredoxin, and ascorbic acid, were identified in the genome of *Colwellia* sp. Arc7-D, a H2O2-resistant psychrophilic bacterium, isolated from Arctic Ocean sediment (Zhang et al., 2019).

### Glaciers

Glaciers, as one of the fastest-disappearing ecosystems, are still waiting to be explored. It is an extremely cold biome, inhabited by unique species of algae, bacteria, fungi and protozoa which had to adapt to these extreme living conditions. They are usually studied in terms of ecology and global warming, but here we would like to point out that this extremely cold biome can be a source of compounds beneficial for humans. It has been shown that glaciers and ice sheets around the world can contain as many as 1010 cells (Irving-Fynn & Edwards, 2014; Anesio et al., 2017). This means that there are many organisms, including but not restricted to microorganisms, in these habitats which are still awaiting to be discovered.

### Compounds with antibacterial and antifungal activities

A fungus called *Geomyces* sp. was discovered, in which derivatives of asterric acid were identified. Asterric acid derivatives are currently used in medicine, between others, to treat the initial stages of pulmonary fibrosis, myocardial infarction or renal insufficiency (Lee et al., 2002). None of the previously discovered derivatives had fungicidal or bactericidal properties similar to these discovered in this fungus. Moreover, following derivatives of asterric acid were found in soil samples in Antarctica: ethyl asterrate, n-butyl asterrate and geomycins A-C. The structures of these metabolites were examined by NMR spectroscopy. Absolute configuration was determined by the CD chiral excitation method. Samples taken in Antarctica from King George Island and grown in fermentation culture on a solid medium, revealed antifungal activity against *Aspergillus fumigatus* and antibacterial activity against *Muphylooccus aurous*, *Streptococcus pneumoniae*, and *Escherichia coli* (Li et al., 2008). The utility of asterric acid and its derivatives in the medical or biotechnological industry may be predicted. An interesting aspect is also the fact that although they are derivatives of one compound, previously unknown properties are being characterized. This is an additional incentive to further search for organisms, and the compounds they produce, for human and medical use.

### Compounds with anticancer activities

Other compounds obtained from organisms living in glacier belong to the group of cytochalasins which are generally known as fungal toxins. Cytochalasins are intensively analyzing in the light of their abilities to inhibit the growth of neoplasms, taking advantage of their cytotoxic effects. A study of cytochalasin from tropical fungi showed that cytochalasin D was effective in inhibiting the proliferation of CT26 colon cancer cells, and that it induced apoptosis in these cells in *in vitro* tests. *In vivo* studies in mice with cancer demonstrated that treating animals with this compound inhibited tumor growth and prolonged the life of sick mice (Huang et al., 2012).

Another example is cytochalasin B which effectively disrupts the formation of actin polymers. This is an important property because compounds that interfere with the proper functioning of the mitotic spindle are considered a valuable group of chemotherapeutic agents. Changes in microtubule functions can enhance the action of division checkpoints, and thus inhibit the progression of the tumor cell cycle (Mukhtar et al., 2014). *In vitro* studies on adherent cell cultures, using M109 lung cancer cells, B16BL5, B16F10 murine melanoma...
cells, and P388/ADR murine leukemia cells, proved that cytochalasin B is indeed cytotoxic to these tumors. This compound, as well as cytochalasin D acting in cooperation with doxorubicin (ADR), work against ADR-resistant P388 leukemia cells. In vitro tests were also performed with intraperitoneal administration of cytochalasins B and D. They prolonged the life expectancy of mice challenged with P388/S and P388/ADR leukemias, and in some cases resulted in long-term survival (Trendowski et al., 2015). Thus, it seems that cytochalasins have a strong anti-cancer activity that may contribute to the treatment of cancer. Additionally, these compounds are able to act synergistically with other drugs, enhancing the effect or showing completely new mechanisms.

In this light, finding a newly discovered cytochalasin A in the glacier seems to be an important finding. A fungus Alternaria alternata, from Midui Glacier in China, produced a compound called alternatiasin A (Guo et al., 2021), a previously unknown pentacyclic cytochalasin. The structure of this compound was investigated using NMR and MS spectroscopy, and by a comparison with data from the literature. Antimicrobial activity against Staphylococcus aureus, Bacillus subtilis, and Escherichia coli were demonstrated. In addition, this compound also exhibited a strong cytotoxic activity to human cell lines (Guo et al., 2021).

This aspect opens many doors for further research by combining the effects of cytochalasines with other therapeutics, to check their properties.

Compounds with antioxidant properties

It is well known that exposure to UV radiation causes DNA damage through oxidative stress due to the production of reactive oxygen species (ROS) which generally include hydrogen peroxide (H₂O₂), hydroxyl radical (OH•), and superoxide anion (O₂•⁻) (Rosic, 2019). Oxidative stress and the resulting oxidative damage are also major contributors to the formation and progression of cancer (Klaunig, 2018).

Organisms from glaciers have developed various adaptation strategies to mitigate the effects of solar radiation, including an avoidance mechanism, the synthesis of substances that absorb UV rays, production of enzymatic and non-enzymatic antioxidants, reactive oxygen species (ROS) quenching, and activation of the DNA repair pathways (Fuentes-Tristan et al., 2019).

Purpurogallin

In the area of the Austrian Alps, a group of algae discovered which include Mesotaenium berggrenia, a species containing a brownish pigment in the peripheral vacuoles (Remias et al., 2009). Similarly, in Ancylonema nordenskiöldii taken from the Svalbard glacier, brownish vacuoles were located around the periphery (Remias et al., 2012a). It was found that this pigment is a derivative of purpurogallin (PPG) and has the ability to absorb ultraviolet light, thus acting photoprotectively (Remias et al., 2012b). PPG has been tested clinically as an inhibitor of pololike kinases, which are often overexpressed in tumors contributing to cancer progression (Liu, 2015). Mesotaenium berggrenia cells that flourish under less UV-irradiated conditions, also contain the dye discussed above, which suggests that this compound may have additional effects on organisms, other than just their photoprotective role, for example bactericidal properties (Anesio et al., 2017).

Astaxanthin

Astaxanthin is a powerful antioxidant found in Chlomyydomonas nivalis algae, and it has been intensively studied in many directions in recent years (Varshney et al., 2015; Dial et al., 2018). Based on its strong antioxidant activity, the beneficial effects of astaxanthin have been found in relation to many human health problems, like disorders of metabolism (Ni et al., 2015), and cognitive functions including, Alzheimer’s and Parkinson’s. It also positively influences mental fatigue (Galasso et al., 2018), skin condition, by reducing skin damage caused by UV light, and it was even proposed to be used in an adjunctive therapy of eye diseases (Yoshihisa et al., 2014; Giannaccare et al., 2020).

Cognitive functions

Studies have been conducted to check whether astaxanthin supplementation, along with another compound – sesamine, is able to improve cognitive functions of people with mild cognitive impairment (MCI). Twenty-one participants with MCI were recruited in a double-blind placebo-controlled pilot study. The results showed that supplementation with astaxanthin and sesamine improved cognitive function and the ability to understand and perform complex tasks quickly and accurately (Ito et al., 2018a).

Skin protection

The use of astaxanthin in the case of skin deterioration, inflammation and disorders caused by exposure to UV light, has been investigated. Administration of astaxanthin-containing liposomes has been shown to prevent the collagen reduction that occurs after exposure to UV light when no other form of protection was used (Hama et al., 2012). The results of a study in which 23 participants were recruited to a 10-week double-blind placebo-controlled study suggested that astaxanthin promotes endogenous antioxidant activity to reduce UV-induced activation of ROS-producing enzymes (Ito et al., 2018b). In addition to its antioxidant and anti-damage abilities, astaxanthin has anti-inflammatory effects. This was demonstrated by results of a treatment that prevented the UV-induced increase in interleukin (IL)-1x, IL-6, IL-8, and tumor necrosis factor (TNF)-α in cultured kerocytes and fibroblasts (Tominaga et al., 2017). This compound has also a beneficial effect in the treatment of atopic dermatitis (Ito et al., 2018b). Therefore, astaxanthin has valuable antioxidant properties, positively influencing the maintenance of healthy skin, and rebuilding its damage. It was proposed to be a very promising compound in dermatology and cosmetology (Singh et al., 2020).

Myccosporine-Like Amino Acids

Another compounds produced by phytoplankton discovered in King George Island in Antarctica are myccosporine-like amino acids (MAAs), the properties of which can be used by humans (Kim et al., 2018). These compounds have a great potential for use in cosmetics, pharmacy, biotechnology and biomedicine, for example as natural substances for use in sunscreen (Núñez-Pons et al., 2018). These compounds occur naturally in glacial cyanobacteria from the genus Lyngbya. Due to their strong free radical scavenging properties, MAA play the role of an antioxidant that suppresses damage caused by singlet oxygen, thus, they have anti-inflammatory and antiaging properties (Fuentes-Tristan et al., 2019). This was demonstrated in in vitro tests with cultured cells, proving that it is a promising group of useful substances (Su et al., 2014; Kageyama & Waditee-Sirisattha, 2019).

An interesting issue that requires further research is the possibility of inhibiting bacterial collagenase, which
is involved in bacterial virulence and takes part in the pathogenic process of *Clostridium* spp. There are studies which show that MAAs do have such an ability, but the exact mechanism is not known yet (Taranuntsuk *et al.*, 2018). Although more research is still needed due to the diversity of structures and activities of these molecules, they may have a value of industrial significance, being natural and environmentally safe substances.

**CONCLUSIONS AND PERSPECTIVES**

In a situation where the drugs that were our salvation stop being effective, we need to act really quickly. There is a strong need to find compounds that will bring something new to the world of science and will be a lifetime for humanity. We need an unconventional action, that is why more and more places are explored that have not yet been extensively studied. They are primarily extreme places due to environmental conditions that prevail there. This review indicates that such studies, although very difficult, bring many new discoveries of compounds that show their possible therapeutic effects in many fields related to human health or in which such potential is evident. These are, for example, compounds such as cervaamin A, B, C, D, and xiakemycin A, extracted from caves, anti-enterococcal cyanobacterium extract and several compounds with antibacterial activity isolated from hot springs, and asterec acid derivatives (ethyl asterric acid) found in glaciers that exhibit antimicrobial activities. Xiakemycin A from caves, cytochalasin A from Midui Glacier in China, carotenoid derivatives isolated from marine areas of Patagonia and Antarctica, cyanobacterium extracts isolated from Polichnitos thermal springs in Greece, or cyanobacterium extracts from caves, cytochalasin A from Midui Glacier in Patgonia and Antarctica, cyanobacterium extracts isolated from hydrothermal vents which appear to have anti-cancer properties are next examples of promising molecules. Anti-inflammatory compounds such as xenocyclin B or compounds with strong anti-oxidant activity, such as purpurogallin or astaxanthin, the latter showing an ability to improve cognitive functions in people with Alzheimer’s and Parkinson’s disease, are other potential goals of other drugs. However, most of these compounds were tested only in *vitro*, thus further, advanced research is necessary, whether in animal models or human subjects. Checking their safety and interactions of these compounds with other drugs are also mandatory. It is definitely a difficult path, but a profitable one, because natural compounds extracted from extreme environments provide a promising source of remedies that we need in the current alarming situation.

**REFERENCES**

Adam D, Maciejewska M, Naźóń A, Martinek L, Coppitiw W, Karim L, Baurain D, Rigali S (2018) Isolation, characterization, and antibacterial activity of hard-to-culture actinobacteria from cave moon-milk deposits. *Antibiotics (Basel)* 7: 28. https://doi.org/10.3390/antibiotics7020028

Ahrniąen SA, Mostafa YS, Al-Qahrani STS, Sahlahji T, Taha TH (2019) Antimicrobial activity and GC-MS analysis of bioactive constituents of thermophilic bacteria isolated from Saudi Hot springs. *Arab J Sci Eng* 44: 75–85. https://doi.org/10.1007/s13369-018-3397-0

Ambrozič Avguštin J, Pešić P, Iasić L (2019) Screening the culturable microbial mats for the production of antimicrobial compounds and antibiotic resistance. *JFI* 48: 295–303. https://doi.org/10.5038/1827-806X.48.3.2272

Anesio AM, Lutz S,Christmas NAM, Benning LG (2017) The microbiome of glaciers and ice sheets. *NPJ Polar Biol Microb* 3: 1–11. https://doi.org/10.1038/s41522-017-0019-0

Ankisetty S, Slattery M (2012) Antibacterial secondary metabolites from the cave sponge Xestospongia sp. *Marine Drugs* 10: 1037–1043. https://doi.org/10.3390/md10051037

Ayub ND, Pettinari MJ, Ruiz JA, López NI (2004) A polyhydroxybutyrate-producing Pseudomonas sp. isolated from Antarctic environments with high stress resistance. *Curr Microbiol* 49: 170–174. https://doi.org/10.1007/s00284-004-4254-2

Balke MM, Leidshöjd SD, Mukherjee PK, Ghanoun MA (2002) Mechanisms of fungal resistance. *Droga* 62: 1025–1040. https://doi.org/10.2165/00003495-200262070-00004

Belyagoubi L, Belyagoubi-Benhammou N, Jurado V, Dupont J, Lacoste S, Djeblah F, Ounadjela F, Benassa S, Habi S, Abdelouahid D, Sani-Jemezene C (2018) Antimicrobial activity of mycosporine-like amino acids (MAAs) and their analogs (actinomycines and fungi) isolated from Chaabe Cave, Algeria. *IJFS* 47: 189–199. https://doi.org/10.5038/1827-806X.47.2.21148

Benammar L, Inan Bektar K, Menashta T, Belduz AO, Guler HJ, Bedia IA, Gonzalez JM, Ayachi A (2020) Diversity and enzymatic potential of thermophilic bacteria associated with terrestrial hot springs in Algeria. *Br J Microbiol* 51: 1987–2007. https://doi.org/10.1016/j.bjm.2020.02.004

Blair JMA, Webber MA, Baylaj AJ, Ogboho DO, Piddock LJ (2015) Molecular mechanisms of antibiotic resistance. *Nat Rev Microbiol* 13: 42–51. https://doi.org/10.1038/nrmicro3380

Borgave SB, Kulkarni MS, Kanekar PP, Naik DG (2017) Alkaliphilic bacteria and thermophilic actinomycetes as new sources of antimicrobial compounds. In *Industrial Biotechnology*, pp 47–49; Apple Academic Press.

Center for Disease Control and Prevention (2019) Antibiotic resistance threats in the United States, 2019. Atlanta, GA: U.S. Department of Health and Human Services: CDC. https://doi.org/10.15620/cdc28532

Chakrabadi N (Ann), Sadowyr T, Rule D, Watson K, Moore P, Soliman L, Azed N, Donkor K, Horne D (2013) Cure from the cave: volcanic cave actinomycines and their potential in drug discovery. *Int J Spherd* 42: 35–47. https://doi.org/10.5038/1827-806X.42.1.5

Derevetski DK, McNeers CR, Sylmam G, Covington GL, Shamugam G, Marnett LJ, Polavarapu BL, Bachmann BO (2014) Structure and stereochemical determination of hypogeanic acids from a cave-derived actinomycete. *J Nat Prod* 77: 1759–1763. https://doi.org/10.1021/np400742p

Dial RJ, Ganey GQ, Skiles SM (2018) What color should glacier algae be? An ecological role for red carbon in the cryosphere. *FEBS Mycobiol Ecol* 94: https://doi.org/10.1007/s10334-016-0724-8

Elasova TŽ, Temirov IV, Sokolov SL, Alakhov IV (2002) Secondary antimicrobial metabolites produced by thermophilic *Bacillus* spp. strains VK2 and VK21. *Prikl Biokhim Mikrobiol* 38: 261–267

Fang W, Lin X, Zhou X, Wan J, Lu X, Yang B, Ai W, Lin J, Zhang F, Tu Z, Liu Y (2014) Cytotoxic and antiviral nitrobenzoyl sesquiphenols from the marine-derived fungus *Aspergillus ochraceus* Je- maIF17. *Med Chem Commun* 5: 701–705. https://doi.org/10.1039/c3md00371

Fuentes-Tristán S, Parra-Saldivar R, Iqbal HMN, Carrillo-Nieves D (2019) Bioinspired biomolecules: Mycosporine-like amino acids and styrrenoids from *Lyngbya* sp. with UV-protection potentials. *J Photochem Photobiol B: Biol* 201: 111684. https://doi.org/10.1016/j.jphotobiol.2019.111684

Galasso C, Orefice I, Pellone P, Miele R, Ianora A, Brunet C, Sansone C (2018) On the neuroprotective role of astaxanthin: new perspectives? *Mar Drugs* 16: 247. https://doi.org/10.3390/md16080247

Ghariat T, Braiek OB, Hani K (2015) Detection and characterization of a bacteriocin, putadicin T01, produced by *Pseudomonas putida* isolated from hot spring water. *APMS* 123: 260–268. https://doi.org/10.1111/apm.12343

Giannareca G, Pellegrini M, Senni C, Bernabei F, Scorcia V, Cicero G, Marnett LJ, Polavarapu PL, Bachmann BO (2014) Structure and stereochemical determination of hypogeanic acids from a cave-derived actinomycete. *J Nat Prod* 77: 1759–1763. https://doi.org/10.1021/np400742p

Giordano D (2020) Bioactive molecules from extreme environments. *Mar Drugs* 18: 640. https://doi.org/10.3390/md18120640

Guo Z, Huo R, Niu S, Liu X, Liu L (2021) Alternariol A, a new pentacene cytochalasin from the fungus *Alternaria alternata*. *J Antibiot* 74: 596–600. https://doi.org/10.1093/antibiotics/abaa044.0

Hraft T, Braiek OB, Hani K (2015) Detection and characterization of a bacteriocin, putadicin T01, produced by *Pseudomonas putida* isolated from hot spring water. *APMS* 123: 260–268. https://doi.org/10.1111/apm.12343

Huang Q, Zhang Y, Shi E, Qu X, Yu D, Chen L, Wang Y, Cao S, Zou Z, Liu Q, Xie C, Shen J (2018) Bicycle spongistatin b from the sponges *Spongia glycoside* complex from a cave bacterium can defeat vancomy-
Biologically active compounds produced by microorganisms from hard-to-reach environments
isolated from Kotumsa Cave of India. Int J Biol Chem 6: 53–60. https://doi.org/10.3932/jbchc2012.53.60

Rangseekaew P, Pathom-aree W (2019) Cave actinobacteria as producers of bioactive metabolites. Frontiers Microbiol 10: 387. https://doi.org/10.3389/fmicb.2019.00387

Remias D, Holzinger A, Lütz C (2009) Physiology, ultrastructure and habitat of the ice alga Mesotaenium berggrenii (Zygnematales, Streptophyta), a brown ice alga on Svalbard (high arctic). Polar Biol 35: 899–908. https://doi.org/10.1007/s00300-011-1135-6

Remias D, Holzinger A, Aigner S, Lütz C (2012a) Ecophysiology and ultrastructure of Anchofora nordensiskii (Zygnematales, Streptophyta), causing brown ice on glaciers in Svalbard (high arctic). Polar Biol 35: 301–312. https://doi.org/10.1007/s00300-016-1732-7

Remias D, Schweiger S, Aigner S, Leta T, Stuppner H, Lütz C (2012b) Characterization of an UV- and VIS-absorbing, purpuragallin-derived secondary pigment new to algae and highly abundant in Mesotaenium berggrenii (Zygnematales, Streptophyta), an extremophile living on glaciers. FEMS Microbiol Ecol 79: 638–648. https://doi.org/10.1111/j.1574-6941.2011.01245.x

Riquelme C, Eines-Dapkevicius M de L, Miller AZ, Charlop-Powers Z, Remias D, Schwaiger S, Aigner S, Leya T, Stuppner H, Lütz C (2012b) Anticancer drug leads? Frontiers Microbiol 3: 899–908. https://doi.org/10.3389/fmicb.2012.00387

Rosic NN (2019) Mycosporine-like amino acids: Making the foundation for organic personalised sunscreens. Mar Drugs 17: 638. https://doi.org/10.3390/md17110638

Sawicka E, Wolniak M, Piszowar A (2018) Mechanisms of cancer multidrug resistance, with special emphasis on breast cancer. Pol J Vet Med 74: 500–504 (in Polish)

Shanker M, Willcutts D, Roth JA, Ramesh R (2010) Drug resistance in lung cancer. Int J Biochem Cell Biol 42: 967–981. https://doi.org/10.1016/j.biocel.2010.01.016

Sood S, Malhotra M, Das BK, Kapil A (2008) Enterococcal infections and antibiotic resistance. Indian J Med Res 128: 111–121

Stankovic N, Radulovic V, Petkovic M, Vuckovic I, Jadranin M, Vasiljevic B, Nikoli Tocevic Runic J (2012) Streptomyces sp. JSS20 produces exceptionally high quantities of unkeediprodigiosin with antibiotic, antiossidative, and UV-protective properties. Appl Microbiol Biotechnol 96: 1217–1231. https://doi.org/10.1007/s00253-012-4257-3

Sah S-S, Hwang J, Park M, Seo HH, Kim H-S, Lee JH, Moh SH, Lee T-K (2014) Anti-inflammation activities of mycostreptomyces-like amino acids (MAAs) in response to UV radiation suggest potential anti-skin aging activity. Mar Drugs 12: 5174–5187. https://doi.org/10.3390/md12105174

Tapia C, López B, Astuya A, Becerra J, Gugliandolo C, Parra B, Martínez M (2019) Antiproliferative activity of carotenoid pigments produced by extremophile bacteria. Nat Prod Lett 31: 1–5. https://doi.org/10.1080/10549856.2018.1572715

Tarasuntisuk S, Patipong T, Hibino T, Waditee-Sirisattha R, Kageyama S (2017) Tarasuntisuk S, Patipong T, Hibino T, Waditee-Sirisattha R, Kageyama Suh S-S, Hwang J, Park M, Seo HH, Kim H-S, Lee JH, Moh SH, Sood S, Malhotra M, Das BK, Kapil A (2017) Novel essential role of ethanol oxidation genes at low temperature revealed by transcriptome analysis in the Antarctic bacterium Pseudomonas extremozonaria. PLoS One 10:e0145353. https://doi.org/10.1371/journal.pone.0145353

Tumbrasri Y, Deseva I, Mihaylova D, Stoyanova M, Krastev I, Nikolova R, Yanakieva V, Ivanov I (2018) Isolation, characterization and amino acid composition of a bacteriocin produced by Bacillus subtilis strain BM47. Food Technol Biotechnol 56: 546–552. https://doi.org/10.17711/fb.06.04.18.5905

Tyagi S, Singh RK, Tiwari SP (2021) Anticientroccocal and anti-oxidative potential of a thermophilic cyanobacterium, Leptolyngbya sp. IJNBGU 003. Saudi J Biol Sci 28: 4022–4028. https://doi.org/10.1016/j.sjbs.2021.04.003

Varshney P, Mikkal P, Vonsbak A, Bear dall J, Wangikar PP (2015) Extreme-microbial micro-algae and their potential contribution in biotechnology. Bioresource Technol 184: 363–372. https://doi.org/10.1016/j.biortech.2014.11.040

Vortskelovskaya IV, Axsenov-Gribanov DV, Murzina SA, Pekloeva SN, Protosov ES, Gamaunov SY, Timofeyev MA (2018) Estimation of antimicrobial activities and fatty acid composition of actinobacteria isolated from water surface of underground lakes from Badzhseyskaya and Olikhotichnya caves in Siberia. Po r: 6. e3852. https://doi.org/10.7717/peernl.3852

White WB, Culver DC, Pipan T (2019) Cave, definition of. In Encyclopedia of Caves. Academic Press

World Health Organization (2020) Global health estimates: Leading causes of death. https://www.who.int/data/gho/data/themes/mortality-and-global-health-estimates/ghe-leading-causes-of-death

Wu G, Sun X, Yu G, Wang W, Zhu T, Gu Q, Li D (2014) Cladosins A-E, hybrid polyketides from a deep-sea-derived fungus, Cladosporium sp. Cell Mol Life Sci 71: 270–275. https://doi.org/10.1007/s00018-014-1088-x

Xu C, Sun X, Jin M, Zhang X (2017) A Novel bensouquione compound isolated from Deep-Sea hydrothermal vent triggers apoptosis of tumor cells. Marine Drugs 15: 200. https://doi.org/10.3390/md15070200

Yoshizawa Y, Rehman MU, Shimizu T (2014) Astaxanthin, a xanthophyll carotenoid, inhibits ultraviolet-induced apoptosis in keratinocytes. Exp Dermatol 23: 178–183. https://doi.org/10.1111/exd.12347

Yucel S, Yamas M (2010) Selection of Streptomyces isolates from Turkish karstic caves against antibiotic resistant microorganisms. Pak J Pharmacol 23: 1–6.

Zhang Z, Li S, Li J, Gu X, Lin X (2019) Complete genome sequences of a H2O2-resistant psychrophile bacterium Colwellia sp. Arc7-D isolated from Arctic Ocean sediment. Marine Genomics 43: 65–67. https://doi.org/10.1016/j.magen.2018.08.001

Zhou X, Fang W, Tan S, Lin X, Xun T, Yang B, Liu S, Liu Y (2016) Aspergillins with anti-HIV-1 activities from the marine-derived fungus Aspergillus niger SC1075. Bioorg Med Chem Lett 26: 361–365. https://doi.org/10.1016/j.bmcl.2015.12.005

Zhou Y, Li Y-H, Yu H-B, Liu X-Y, Lu X-L, Jiao B-H (2018) Furancione derivative and sesquiterpene from Antarctic marine-derived fungus Penicillium sp. S-1-18. J Asian Nat Prod Res 20: 1108–1115. https://doi.org/10.1080/12221153.2017.1385604

Zhu T, Chen Z, Liu P, Wang Y, Xin Z, Zhu W (2014) New nribolides from the marine-derived fungus Aspergillus terreus OUCMDZ-1925. J Antibiot 67: 315–318. https://doi.org/10.1038/ja.2013.135