ACTA ABP BIOCHIMICA POLONICA

Vol. 68, No 4/2021
565–574
https://doi.org/10.18388/abp.2020_5887

Review

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

Zuzanna Cyske[1]*, Weronika Jaroszewicz[1]*, Magdalena Żabińska[1], Patryk Lorenc[1], Maja Sochocka[1], Patrycja Bielańska[1], Łukasz Grabowski[2], Lidia Gaffke[1], Karolina Pierzynowska[1] and Grzegorz Węgrzyn[1]✉

[1]Department of Molecular Biology, University of Gdansk, Gdańsk, Poland; [2]Laboratory of Phage Therapy, Institute of Biochemistry and Biophysics, Polish Academy of Sciences, Gdańsk, Poland

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

Received: 11 September, 2021; revised: 12 September, 2021; accepted: 14 September, 2021; available on-line: 19 September, 2021

✉e-mail: grzegorz.wegrzyn@ug.edu.pl
*Equal contribution

Abbreviations: ADR, doxorubicin; ATTC, American Type Culture Collection; CD, circular dichroism; CPE, cytopathic 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 resonsnce; PBMC, peripheral blood mononuclear cells; PNPP, *p*-nitrophenyl phosphate; PPG, purpurogallin; ROS, reactive oxygen species; UV, ultraviolet; VRE, vancomycin-resistant Enterobacter

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) *Clostridioides 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.

COMPOUNDS 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 theromophiles (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 subbrevis*, *O. tenius*, *O. limentica*, *O. angusta*, *O. articulate*, *Synechocystis aquatilis*, and *Synechoccous cerdorum* (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*, *Brochotrix thermosphacta*, *Yersinia enterocolitica*, *Hafnia* sp., *Salmonella enterica*, *Bacillus megaterium*, *Enterococcus faecalis* 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 isolates were antagonistic against all of these pathogens. Genetic sequencing and phylogenetic analysis led to their identification as *Bacillus sonorensis, Bacillus thermocopriae, Brevibacillus borstelensis* and *Brevibacillus parabrevis*. Cell-free extracts GC-MS analysis of secondary metabolites detected 40 of them among which there were mephensin, cyclohexyl acrylate, (3-aminopropyl) dibutylborane (*B. sonorensis*); etomidate, L-menthyl lactate, (3-aminopropyl) dibutylboran (*B. borstelensis*); tabtoxinine-β-lactame, nicotinyl alcohol (*B. parabrevis*); cyclohexyl acrylate, imiloxan (*B. thermocopriae*). 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 methylotropicus* strain BM47 isolated from a thermal spring in Bulgaria, a peptide synthetized by this species was characterized as a bacteriocin. *In vitro* screening of *B. methylotropicus* 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., *Aspergillus 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

29213 and *B. cereus* ATCC 11778 (Hussein *et al.*, 2018). Actinobacteria are well known for antibiotic production ability which include streptomycin, streptothricin and actinomycin (Madigan *et al.*, 2009). This proves that newly detected Actinobacteria are also a good source to discover and develop new antibiotics (Hussein *et al.*, 2018).

The latest reports also brought information about a thermophilic cyanobacterium, *Leptolyngbia* sp. HNBGU 003, isolated from Taptkund hot spring in Himalaya (India) which showed to be a source of anti-enterococcal extracts (Tyagi *et al.*, 2021). Enterococci are a group of food-borne pathogens known for causing bloodstream infections (Oprea & Zervos, 2007), urinary tract infections, sepsis and endocarditis (Sood *et al.*, 2008). They have also developed a multidrug resistance that leaves very narrow spectrum of antibiotic treatment of enterococci caused infections (Karaiskos *et al.*, 2019). The anti-enterococcal activity of extracts from the isolated cyanobacterium was tested by the agar well diffusion method against multidrug-resistant and -sensitive strains of *Enterococcus faecium*. Seventy two percent of *Leptolyngbia* sp. HNBGU 003 extracts showed antibacterial activity against both strains. Diethyl ether extract (DEEL-3) inhibited enterococcal growth with the lowest concentration. The GC-MS analysis of DEEL-3 has revealed two main phenolic compounds, phenol, 2,4-bis(1,1-dimethylethyl)-, phosphite (3:1) and tris(2,4-di-tert-butylphenyl) phosphate. Further investigations may reveal if these two compounds, which can be used as food additives, are responsible for DEEL-3 anti-enterococcal activity (Tyagi *et al.*, 2021).

Compounds with antiviral activities

An extracellular polysaccharide (EPS-2), produced by *Geobacillus thermodenitrificans* strain B3-72 isolated from a shallow marine vent of Vulcano Island (Italy), showed to have the immunomodulatory and antiviral properties. Human peripheral blood mononuclear cells (PBMC) were seeded, treated with several concentrations of EPS-2 and infected with HSV-2 virus. The results of plaque reduction assay exhibited that high concentrations of EPS-2 inhibited HSV-2 replication and increased the inflammatory response supported by Th-1 cytokines, including IL-12, IL-18, FN-γ, IFN-α, and TNF-α. However, lower concentrations of EPS-2 did not affect HSV-2 replication, and the cytokine evaluations have shown it still stimulates inflammatory response. These results showed the potential way of EPS-2 use for the therapeutic manipulation of immune response in viral infections (Arena *et al.*, 2009).

Compounds with anticancer activities

An interesting research on *Cyanobacterium* sp. collected at Polichnitos (Greece) hot spring has revealed its anticancer activity. Plasmid analysis revealed a 99% identity of *Cyanobacterium sp.* with *Cyanobacterium aponinum* type strain. The culture broth activity against PC3 human prostate cancer cell line was measured using crystal violet and MTT assays. Both of them revealed a strong, correlated to dose, toxicity against PC3 cells, while they have shown a relatively low toxicity to human endothelial cells. Extracellular extract of a newly isolated *Cyanobacterium sp.* has also exhibited a strong insecticidal activity against *Aedes aegypti* larvae which is a vector of many serious human diseases, including dengue fever and yellow fever viruses. Thus, the extract may be potentially used as a natural, bioactive insecticide (Mizerakis *et al.*, 2017).

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, depigmented 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 iron 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, Agromyces, Nocardia, Rhodococcus, Micrococcus* 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* HKI 0179, proved to be responsible for antibacterial activities against multidrug-resistant *Staphylococcus aureus* and vancomycin-resistant *Enterococcus faecalis* strains (Herold *et al.*, 2005). 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 PNK470 and PT708 showed activities against Gram-positive bacteria *Bacillus cereus*, methicillin-resistant *Staphylococcus aureus* (MRSA) and *Paenibacillus lavae* (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 *Streptomycetes* 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* ATTC 25922, *Fusarium culmorum, Fusarium moniliforme*, MRSA, vancomycin resistant *Enterobacter faecium* (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 *Mycobacterium intracellulare*. Moreover, undecylprodigiosin isolated from *Streptomyces* sp. JS520, has antibacterial activities against *Micrococcus luteus* and *Bacillus subtilis* (Stankovic *et al.*, 2012). An antibacterial activity against *Bacillus cereus* TISTR 687, methicillin-resistant *Staphylococ-*

cus aureus and *Paenibacillus* larvae LMG 9820T isolates from Actinomycete strain PT708T, classified as the *Nonomuria* genus, was collected from cave soil in Thailand (Nakaew *et al*., 2012). Then, *Streotomyces* isolates from Kotumsar cave (India) were tested against *Escherichia coli* MTCC 1667, *Staphylococcus aureus* MTCC 96, and *Pseudomonas aeruginosa* JNMC. A *Streptomyces roseus* (KCA13) isolate showed a strong antibacterial activity against *E. coli* and *P. aerouginosa* (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 isolates were tested against *Bacillus subtilis* ATCC 6633, *Pseudomonas aeruginosa* NBIMCC 1390, *Xanthomonas oryzae*, and *Rhodotorula mucilaginosa* 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 volcanic cave. Eight two of them were randomly selected to gene sequencing which revealed that almost 80% strains belonged to the *Streptomyces* 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 β-lactamase of *Eschierichia coli*, MRSA, *Acinetobacter 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*, *Staphylococcus aureus*, *Escherichia coli*, *Pseudomonas aeruginosa*, *Listeria monocytogenes,* and *Listeria innocua* (Riquelme *et al*., 2017).

Compounds named hypogeamicins B−D, isolated from *Nonomuraea specus*, and lipids extracted from two cyanobacteria (*Toxopsis calypsus* strain ATHU-CY 3314 and *Phormidium melanochroun* strain ATHU-CY 3315) were also tested for antibacterial activities. Their extracts inhibited growth of *Bacillus subtilis*, *Enterococcus faecium*, and *Enterococcus faecalis* (Derewacz *et al*., 2014; Lamprinou *et al*., 2015). Xiakemycin A, isolated from *Streptomyces* sp. CC8-201, has also strong activities against *Staphylococcus aureus, Staphylococcus epidermidis, Enterococcus faecalis*, and *Enterococcus faecium* (Jiang *et al*., 2015).

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 bacteria. For two very active strains (1350R2-TSA30-6 and 1410WF1-TSA30-2), chemical structures of the main compounds were determined and they were pyrrolopyrazines pyrrolo[1,2-a]pyrazine-1,4-dione, hexahydro-3-(2-methylpropyl) and pyrrolo[1,2-a]pyrazine -1,4-dione, hexahydro-3-(phenylmethyl) (for 1350R2-TSA30-6 strain), and 1,2-benzenedicarboxylic acid, bis(2-methylpropyl) ester (for 1410WF1-TSA30-2 strain) (Klusaite *et al*., 2016). Seventy eight isolates from genus *Streptomyces* from cave moonmilk deposits were screened for their activities against microbes, *Escherichia coli, Pseudomonas aeruginosa, Citrobacter freundii, Klebsiella pneumoniae, Bacillus subtilis, Staphylococcus aureus*, *Micrococcus luteus, Candida albicans*, *Aspergillus fumigatus, Rasamsonia argillacea, Penicillium 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 *Rasamsonia argillacea* (Maciejewska *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, Nocardia, Rhodococcus*, and *Streptomycetes*. Antibacterial activities of these isolates were tested using Gram-positive and Gram-negative bacteria, including *Escherichia coli, Pseudomonas 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-postive and Gram-negative bacteria, 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. pneumonia*, and *C. albicans* (Belyagoubi *et al*., 2018).

Recent studies were conducted by Ambrožič 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 bacteria. Between 10 and 25% of isolates were active against *B. subtilis*, MRSA, *S. pseudointermedius*, *E. coli,* and *Sallmonella enterica* (Ambrožič 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, Escherichia coli,* clinical *Klebsiella* strains CK1, KC2, and CK3, and three *Enterococcus faecium* strains (19040 E1, E2, E3) (Paun *et al*., 2021).

Compounds with anticancer activities

Actinomycetes strains (377 isolates) were collected from a Thailand cave, and almost 44% of them were non-streptomycetes. Eleven randomly selected isolates from nonstreptomycete isolates were tested against cancer cell lines. Isolate PNK470 and PT708 showed activity against small cell lung cancer (NCI-H187) and oral cavity cancer (KB) (Nakaew *et al*., 2009b). The actinomycete strain PT708T, classified as the *Nonomuria* genus, isolated from a cave soil in Thailand, was effective against lung cancer and oral cavity cancer cells (Nakaew *et al*., 2012).

Three isolated compounds, hypogeamicin A, xiakemycin A, and huanglongmycin A, B and C were also characterized as possessing anti-tumor activities. Hypogeamicin A, isolated from bacterium *Nonomuraea specus,* showed an activity against human colon cancer cell line (TCT-1), but its activity was significantly lower than a previously known cancer drug – paclitaxel (Derewacz *et al*., 2014). Xiakemycin A, isolated from *Streptomyces* sp. CC8-201, had cytotoxicity against 8 cancer cell lines: human lung cancer (A549), breast cancer (MCF-7), hepatoma (HepG-2), cervical cancer (HeLa), colon carcinoma (HCT-116) p53 wt cells, neuroblastoma (SH-SY5Y), and

human prostate cancer (PC-3). The highest cytotoxicity was observed for the first three cancer 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 xenocyloin B, isolated from *Streptomyces* sp. CB09001, has a strong anti-inflammatory effect. Tests conducted on murine macrophage RAW264.7 cell line showed that it can inhibit about 70% of *iNOS* gene expression when applied at 20 μM (Jiang *et al.*, 2019). Furthermore, undecylprodigiosin isolated from *Streptomyces* sp. JS520 expressed antioxidative activities in terms of inhibiting autooxidation of linoleic acid (Stankovic *et al.*, 2012).

COMPOUNDS 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 caboxamycin, 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 showed against the Gram-positive bacteria *Bacillus subtilis* and *Staphylococcus lentus,* 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 albinus* 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 antifungal 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 (Voytsekhovskaya *et al.*, 2018).

The synthesis of silver nanoparticles (AgNPs) by the Gram-negative *Pseudomonas* strain, isolated from the Antarctic marine ciliate *Euplotes focardii,* 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 ($AgNO_3$), 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 terreus* OUCMDZ-1925, found in *Chelon haematocheilus* 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).

The antiviral compound named 6b,9a-dihydroxy-14-p-nitrobenzoylcinnamolide was isolated from the marine-derived fungus *Aspergillus ochraceus* Jcma1F17, cultured from the marine alga *Coelarthrum* sp., collected in Paracel Islands, 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).

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

Marine habitats offer an enormous sources of potential anti-HIV compounds. An example is 2-benzylpyridin-4-one-containing metabolites, aspernigrin 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 which exhibited significant HIV-1 inhibitory activities (Zhou *et al.*, 2016). Moreover, it was found that an ergostane analogue, 3β-hydroxyergosta-8,14,24(28)-trien-7-one, obtained from the marine-derived fungus *Penicillium* sp. IMB17-046, showed anti-HIV activity with an IC50 value of 3.5 μM (Li *et al.*, 2019b).

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 (Lin *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, guignarderemophilane 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-hydroxyquinaldic acid derivative, was isolated from *Streptomyces cyaneofuscatus* M-157, occurring in the deep sea at 1800 m depth in the central Cantabrian Sea. This compound showed cytotoxic 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 alkaloids, (–) – discorhabdin L, (+) – discorhabdin A, and (+) – discorhabdin Q, and three previously unknown discorhabdin analogs, (–) – 2-bromo-discorhabdin D, (–) – 1-acetyl-discorhabdin L, and (+) – 1-octacosatrienoyl-discorhabdin L, extracted from a sponge *Latrunculia biformis* 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 extremaustralis, 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 polyhydroxyalkanoates (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 H_2O_2-resistant psychrophilic bacterium, isolated from Arctic Ocean sediment (Zhang *et al*., 2019).

COMPOUNDS PRODUCED BY MICROORGANISMS FROM 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 10^{29} cells (Irvine-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 *Staphylococcus aureus*, *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 vivo* 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 alternariasin 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. Antibacterial 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 (H_2O_2), hydroxyl radical (OH•), and superoxide anion ($O_2^{\bullet -}$) (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 was 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 polo-like 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 *Chlamydomonas 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)-1α, IL-6, IL-8, and tumor necrosis factor (TNF)-α in cultured keranocytes 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).

Mycosporine-Like Amino Acids

Another compounds produced by phytoplankton discovered in King George Island in Antarctica are micosporine-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 (Suh *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 (Tarasuntisuk *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 compunds that will bring something new to the world of science and will be a lifeline 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 cervamicin 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 asterric acid derivatives (ethyl asterrate, n-butyl asterrate, and geomycins A-C) 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 Patgonia and Antarctica, cyanobacterium extracts isolated from Polichnitos thermal springs in Greece, or compounds isolated from hydrothermal vents which appear to have anti-cancer properties are next examples of promissing molecules. Anti-inflammatory compounds such as xenocyloin B or compounds with strong antioxidant 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 groups of potential 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, Naômé A, Martinet L, Coppieters W, Karim L, Baurain D, Rigali S (2018) Isolation, characterization, and antibacterial activity of hard-to-culture actinobacteria from cave moonmilk deposits. *Antibiotics (Basel)* **7**: 28. https://doi.org/10.3390/antibiotics7020028

Alrumman SA, Mostafa YS, Al-Qahtani STS, Sahlabji 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/s13369-018-3597-0

Ambrožič Avguštin J, Petrič P, Pašić L (2019) Screening the cultivable cave microbial mats for the production of antimicrobial compounds and antibiotic resistance. *IJS* **48**: 295–303. https://doi.org/10.5038/1827-806X.48.3.2272

Anesio AM, Lutz S, Chrismas NAM, Benning LG (2017) The microbiome of glaciers and ice sheets. *NPJ Biofilms Microbiomes* **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

Balkis MM, Leidich SD, Mukherjee PK, Ghannoum MA (2002) Mechanisms of fungal resistance. *Drugs* **62**: 1025–1040. https://doi.org/10.2165/00003495-200262070-00004

Belyagoubi L, Belyagoubi-Benhammou N, Jurado V, Dupont J, Lacoste S, Djebbah F, Ounadjela F, Benaissa S, Habi S, Abdelouahid D, Saiz-Jimenez C (2018) Antimicrobial activities of culturable microorganisms (actinomycetes and fungi) isolated from Chaabe Cave, Algeria. *IJS* **47**: 189–199. https://doi.org/10.5038/1827-806X.47.2.2148

Benammar L, İnan Bektaş K, Menasria T, Beldüz AO, Güler HI, Bedaida IK, Gonzalez JM, Ayachi A (2020) Diversity and enzymatic potential of thermophilic bacteria associated with terrestrial hot springs in Algeria. *Braz J Microbiol* **51**: 1987–2007. https://doi.org/10.1007/s42770-020-00376-0

Blair JMA, Webber MA, Baylay AJ, Ogbolu DO, Piddock LJV (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/cdc:82532

Cheeptham N (Ann), Sadoway T, Rule D, Watson K, Moote P, Soliman L, Azad N, Donkor K, Horne D (2013) Cure from the cave: volcanic cave actinomycetes and their potential in drug discovery. *Int J Speleol* **42**: 35–47. https://doi.org/10.5038/1827-806X.42.1.5

Derewacz DK, McNees CR, Scalmani G, Covington CL, Shanmugam G, Marnett LJ, Polavarapu PL, Bachmann BO (2014) Structure and stereochemical determination of hypogeamicins 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. *FEMS Microbiol Ecol* **94**: https://doi.org/10.1093/femsec/fiy007

Esikova TZ, Temirov IV, Sokolov SL, Alakhov IB (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 T, Tu Z, Liu Y (2014) Cytotoxic and antiviral nitrobenzoyl sesquiterpenoids from the marine-derived fungus *Aspergillus ochraceus* Jcma1F17. *Med Chem Commun* **5**: 701–705. https://doi.org/10.1039/C3MD00371J

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

Galasso C, Orefice I, Pellone P, Cirino 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

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

Giannaccare G, Pellegrini M, Senni C, Bernabei F, Scorcia V, Cicero AFG (2020) Clinical applications of astaxanthin in the treatment of ocular diseases: Emerging insights. *Marine Drugs* **18**: 239. https://doi.org/10.3390/md18050239

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) Alternariasin A, new pentacyclic cytochalasin from the fungus Alternaria alternate. *J Antibiot* **74**: 596–600. https://doi.org/10.1038/s41429-021-00443-0

Hama S, Takahashi K, Inai Y, Shiota K, Sakamoto R, Yamada A, Tsuchiya H, Kanamura K, Yamashita E, Kogure K (2012) Protective effects of topical application of a poorly soluble antioxidant astaxanthin liposomal formulation on ultraviolet-induced skin damage. *J Pharm Sci* **101**: 2909–2916. https://doi.org/10.1002/jps.23216

Heidari F, Riahi H, Yousefzadi M, Asadi M (2012) Antimicrobial activity of cyanobacteria isolated from hot spring of Geno. *Middle East J Sci Res* **12**: 336–339. https://doi.org/10.5829/idosi.mejsr.2012.12.3.64169

Herold K, Gollmick FA, Groth I, Roth M, Menzel K-D, Möllmann U, Gräfe U, Hertweck C (2005) Cervimycin A-D: a polyketide glycoside complex from a cave bacterium can defeat vancomy-

cin resistance. *Chemistry* **11**: 5523–5530. https://doi.org/10.1002/chem.200500320
Hohmann C, Schneider K, Bruntner C, Irran E, Nicholson G, Bull AT, Jones AL, Brown R, Stach JEM, Goodfellow M, Beil W, Krämer M, Imhoff JF, Süssmuth RD, Fiedler H-P (2009) Caboxamycin, a new antibiotic of the benzoxazole family produced by the deep-sea strain *Streptomyces* sp. NTK 937. *J Antibiot (Tokyo)* **62**: 99–104. https://doi.org/10.1038/ja.2008.24
Holohan C, Van Schaeybroeck S, Longley DB, Johnston PG (2013) Cancer drug resistance: an evolving paradigm. *Nat Rev Cancer* **13**: 714–726. https://doi.org/10.1038/nrc3599
Huang F-Y, Li Y-N, Mei W-L, Dai H-F, Zhou P, Tan G-H (2012) Cytochalasin D, a tropical fungal metabolite, inhibits CT26 tumor growth and angiogenesis. *Asian Pac J Trop Med* **5**: 169–174. https://doi.org/10.1016/S1995-7645(12)60019-4
Hussein EI, Jacob JH, Shakhatreh MAK, Al-Razaq MAA, Juhmani A-SF, Cornelison CT (2018) Detection of antibiotic-producing Actinobacteria in the sediment and water of Ma'in thermal springs (Jordan). *Germs* **8**: 191–198. https://doi.org/10.18683/germs.2018.1146
Irvine-Fynn TDL, Edwards A (2014) A frozen asset: the potential of flow cytometry in constraining the glacial biome. *Cytometry A* **85**: 3–7. https://doi.org/10.1002/cyto.a.22411
Ito N, Saito H, Seki S, Ueda F, Asada T (2018a) Effects of composite supplement containing astaxanthin and sesamin on cognitive functions in people with mild cognitive impairment: A randomized, double-blind, placebo-controlled trial. *J Alzheimers Dis* **62**: 1767–1775. https://doi.org/10.3233/JAD-170969
Ito N, Seki S, Ueda F (2018b) The protective role of astaxanthin for UV-induced skin deterioration in healthy people – A randomized, double-blind, placebo-controlled trial. *Nutrients* **10**: 817. https://doi.org/10.3390/nu10070817
Jiang L, Pu H, Xiang J, Su M, Yan X, Yang D, Zhu X, Shen B, Duan Y, Huang Y (2018) Huanglongmycin A-C, cytotoxic polyketides biosynthesized by a putative type II polyketide synthase from *Streptomyces* sp. CB09001. *Front Chem* **6**: 254. https://doi.org/10.3389/fchem.2018.00254
Jiang L, Pu H, Qin X, Liu J, Wen Z, Huang Y, Xiang J, Xiang Y, Ju J, Duan Y, Huang Y (2019) Syn-2, 3-diols and anti-inflammatory indole derivatives from *Streptomyces* sp. CB09001. *Nat Product Res* **35**: 1–8. https://doi.org/10.1080/14786419.2019.1611812
Jiang Z, Guo L, Chen C, Liu S, Zhang L, Dai S, He Q, You X, Hu X, Tuo L, Jiang W, Sun C (2015) Xiakemycin A, a novel pyranonaphthoquinone antibiotic, produced by the *Streptomyces* sp. CC8-201 from the soil of a karst cave. *J Antibiot (Tokyo)* **68**: 771–774. https://doi.org/10.1038/ja.2015.70
John MS, Nagoth JA, Ramasamy KP, Mancini A, Giuli G, Natalello A, Ballarini P, Miceli C, Pucciarelli S (2020) Synthesis of bioactive silver nanoparticles by a pseudomonas strain associated with the antarctic psychrophilic protozoon *Euplotes focardii*. *Mar Drugs* **18**: 38. https://doi.org/10.3390/md18010038
Kageyama H, Waditee-Sirisattha R (2019) Antioxidative, anti-inflammatory, and anti-aging properties of mycosporine-like amino acids: Molecular and cellular mechanisms in the protection of skin-aging. *Mar Drugs* **17**: 222. https://doi.org/10.3390/md17040222
Karaiskos I, Lagou S, Pontikis K, Rapti V, Poulakou G (2019) The "old" and the "new" antibiotics for MDR gram-negative pathogens: for whom, when, and how. *Frontiers in Public Health* **7**: 151. https://doi.org/10.3389/fpubh.2019.00151
Kim BK, Joo H, Lee B, Lee D-H, Ahn I-Y, Ha S-Y (2018) Physiological characteristics and related biochemical parameters of snow algae from King George island, Antarctica. *Ocean Sci J* **53**: 621–630. https://doi.org/10.1007/s12601-018-0053-8
Klaunig JE (2018) Oxidative stress and cancer. *Curr Pharm Des* **24**: 4771–4778. https://doi.org/10.2174/1381612825666190215121712
Klusaite A, Vickackaite V, Vaitkeviciene B, Karnickaite R, Bukelskis D, Kieraite-Aleksandrova I, Kuisiene N (2016) Characterization of antimicrobial activity of culturable bacteria isolated from Krubera-Voronja Cave. *Int J Speleol* **45**: 275–287. https://doi.org/10.5038/1827-806X.45.3.1978
Kumar S, Dangi AK, Shukla P, Baishya D, Khare SK (2019) Thermozymes: Adaptive strategies and tools for their biotechnological applications. *Bioresour Technol* **278**: 372–382. https://doi.org/10.1016/j.biortech.2019.01.088
Lamprinou V, Tryfinopoulou K, Velonakis E, Vatopoulos A, Antonopoulou S, Fragopoulou E, Pantazidou A, Economou-Amilli A (2015) Cave Cyanobacteria showing antibacterial activity. *Int J Speleol* **44**: 231–238. https://doi.org/10.5038/1827-806X.44.3.2
Lee HJ, Lee JH, Hwang BY, Kim HS, Lee JJ (2002) Fungal metabolites, asterric acid derivatives inhibit vascular endothelial growth factor (VEGF)-induced tube formation of HUVECs. *J Antibiot (Tokyo)* **55**: 552–556. https://doi.org/10.7164/antibiotics.55.552
Li F, Peifer C, Janussen D, Tasdemir D (2019a) New discorhabdin alkaloids from the Antarctic deep-sea sponge *Latrunculia biformis*. *Mar Drugs* **17**: 439. https://doi.org/10.3390/md17080439
Li J, Wang Y, Hao X, Li S, Jia J, Guan Y, Peng Z, Bi H, Xiao C, Cen S, Gan M (2019b) Broad-spectrum antiviral natural products from the marine-derived *Penicillium* sp. IMB17-046. *Molecules* **24**: 2821. https://doi.org/10.3390/molecules24152821
Li Y, Sun B, Liu S, Jiang L, Liu X, Zhang H, Che Y (2008) Bioactive asterric acid derivatives from the Antarctic ascomycete fungus *Geomyces* sp. *J Nat Prod* **71**: 1643–1646. https://doi.org/10.1021/np8003003
Lin A, Wu G, Gu Q, Zhu T, Li D (2014) New eremophilane-type sesquiterpenes from an Antarctic deepsea derived fungus, *Penicillium* sp. PR19 N-1. *Arch Pharm Res* **37**: 839–844. https://doi.org/10.1007/s12272-013-0246-8
Liu X (2015) Targeting polo-like kinases: A promising therapeutic approach for cancer treatment. *Transl Oncol* **8**: 185–195. https://doi.org/10.1016/j.tranon.2015.03.010
López NI, Pettinari MJ, Stackebrandt E, Tribelli PM, Põtter M, Steinbüchel A, Méndez BS (2009) *Pseudomonas extremaustralis* sp. nov., a Poly(3-hydroxybutyrate) producer isolated from an antarctic environment. *Curr Microbiol* **59**: 514–519. https://doi.org/10.1007/s00284-009-9469-9
Maciejewska M, Adam D, Martinet L, Naômé A, Calusińska M, Delfosse P, Carnol M, Barton HA, Hayette M-P, Smargiasso N, De Pauw E, Hanikenne M, Baurain D, Rigali S (2016) A Phenotypic and genotypic analysis of the antimicrobial potential of cultivable streptomyces isolated from cave moonmilk deposits. *Front Microbiol* **7**: 1455. https://doi.org/10.3389/fmicb.2016.01455
Madigan MT, Martinko J, Brock T, Dunlap P, Clark DP (2009) *Brock Biology of Microorganisms*. 12th edn. San Francisco, CA: Pearson/Benjamin Cummings
Mahajan GB, Balachandran L (2017) Sources of antibiotics: Hot springs. *Biochem Pharmacol* **134**: 35–41. https://doi.org/10.1016/j.bcp.2016.11.021
Mizerakis P, Stathopoulou P, Tsiamis G, Baeshen MN, Mahyoub JA, Elazzazy AM, Bellou S, Sakoulogeorga E, Triantaphyllidou I-E, Mazioti T, Katsoris P, Aggelis G (2017) Bacterial diversity of the outflows of a Polichnitos (Lesvos, Greece) hot spring, laboratory studies of a *Cyanobacterium* sp. strain and potential medical applications. *Ann Microbiol* **67**: 643–654. https://doi.org/10.1007/s13213-017-1293-z
Mukhtar E, Adhami VM, Mukhtar H (2014) Targeting microtubules by natural agents for cancer therapy. *Mol Cancer Ther* **13**: 275–284. https://doi.org/10.1158/1535-7163.MCT-13-0791
Nakaew N, Sungthong R, Yokota A, Lumyong S (2012) Nonomuraea monospora sp. nov., an actinomycete isolated from cave soil in Thailand, and emended description of the genus Nonomuraea. *Int J Syst Evol Microbiol* **62**: 3007–3012. https://doi.org/10.1099/ijs.0.035220-0
Nakaew N, Pathom-Aree W, Lumyong S (2009a) First record of the isolation, identification and biological activity of a new strain of *Spirillospora albida* from Thai Cave soil. **23**: 1–7. https://doi.org/10.3209/SAJ.SAJ230102
Nakaew N, Pathom-Aree W, Lumyong S (2009b) Generic diversity of rare actinomycetes from Thai Cave soils and their possible use as new bioactive compounds. *Actinomycetologica* **23**: 21–26. https://doi.org/10.3209/saj.SAJ230201
Ni Y, Nagashimada M, Zhuge F, Zhan L, Nagata N, Tsutsui A, Nakanuma Y, Kaneko S, Ota T (2015) Astaxanthin prevents and reverses diet-induced insulin resistance and steatohepatitis in mice: A comparison with vitamin E. *Sci Rep* **5**: 17192. https://doi.org/10.1038/srep17192
Núñez-Pons L, Avila C, Romano G, Verde C, Giordano D (2018) UV-Protective compounds in marine organisms from the Southern Ocean. *Marine Drugs* **16**: 336. https://doi.org/10.3390/md16090336
Oprea SF, Zervos MJ (2007) Enterococcus and its association with foodborne illness. In *Foodborne Diseases*. Simjee S ed, pp 157–174. Totowa, NJ: Humana Press. https://doi.org/10.1007/978-1-59745-501-5_6
Ortiz-López FJ, Alcalde E, Sarmiento-Vizcaíno A, Díaz C, Cautain B, García LA, Blanco G, Reyes F (2018) New 3-hydroxyquinaldic acid derivatives from cultures of the marine derived actinomycete *Streptomyces cyaneofuscatus* M-157. *Mar Drugs* **16**: 371. https://doi.org/10.3390/md16100371
Paun VI, Lavin P, Chifiriuc MC, Purcarea C (2021) First report on antibiotic resistance and antimicrobial activity of bacterial isolates from 13,000-year old cave ice core. *Sci Rep* **11**: 514. https://doi.org/10.1038/s41598-020-79754-5
PharmaMar (2020) *Multicenter, Randomized, Parallel and Proof of Concept Study to Evaluate the Safety Profile of Three Doses of Plitidepsin in Patients With COVID-19 Requiring Hospitalization*. https://clinicaltrials.gov/ct2/show/NCT04382066
Protasov ES, Axenov-Gribanov DV, Rebets YV, Voytsekhovskaya IV, Tokovenko BT, Shatilina ZM, Luzhetskyy AN, Timofeyev MA (2017) The diversity and antibiotic properties of actinobacteria associated with endemic deepwater amphipods of Lake Baikal. *Antonie Van Leeuwenhoek* **110**: 1593–1611. https://doi.org/10.1007/s10482-017-0910-y
Rajput Y, Biswas J, Rai V (2012) Potentiality test in antimicrobial activity and antibiotic sensitivity of subterranean *Streptomyces* strains

isolated from Kotumsar Cave of India. *Int J Biol Chem* **6**: 53–60. https://doi.org/10.3923/ijbc.2012.53.60

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* (Zygnemaphyceae, Chlorophyta) from glaciers in the European Alps. *Phycologia* **48**: 302–312. https://doi.org/10.2216/08-13.1

Remias D, Holzinger A, Aigner S, Lütz C (2012a) Ecophysiology and ultrastructure of *Ancylonema nordenskiöldii* (Zygnematales, Streptophyta), causing brown ice on glaciers in Svalbard (high arctic). *Polar Biol* **35**: 899–908. https://doi.org/10.1007/s00300-011-1135-6

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

Riquelme C, Enes Dapkevicius M de L, Miller AZ, Charlop-Powers Z, Brady S, Mason C, Cheeptham N (2017) Biotechnological potential of actinobacteria from Canadian and Azorean volcanic caves. *Appl Microbiol Biotechnol* **101**: 843–857. https://doi.org/10.1007/s00253-016-7932-7

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, Piwowar A (2018) Mechanisms of cancer multidrug resistance, with special emphasis on breast cancer. *Farm Pol* **74**: 500–504 (in Polish)

Shanker M, Willcutts D, Roth JA, Ramesh R (2010) Drug resistance in lung cancer. *Lung Cancer (Auckl)* **1**: 23–36

Singh KN, Patil S, Barkate H (2020) Protective effects of astaxanthin on skin: Recent scientific evidence, possible mechanisms, and potential indications. *J Cosmet Dermatol* **19**: 22–27. https://doi.org/10.1111/jocd.13019

Sivalingam P, Hong K, Pote J, Prabakar K (2019) Extreme environment *Streptomyces*: Potential sources for new antibacterial and anticancer drug leads? *Int J Microbiol* **2019**: 5283948. https://doi.org/10.1155/2019/5283948

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

Stankovic N, Radulovic V, Petkovic M, Vuckovic I, Jadranin M, Vasiljevic B, Nikodinovic-Runic J (2012) *Streptomyces* sp. JS520 produces exceptionally high quantities of undecylprodigiosin with antibacterial, antioxidative, and UV-protective properties. *Appl Microbiol Biotechnol* **96**: 1217–1231. https://doi.org/10.1007/s00253-012-4237-3

Suh S-S, Hwang J, Park M, Seo HH, Kim H-S, Lee JH, Moh SH, Lee T-K (2014) Anti-inflammation activities of mycosporine-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 Res*1–5. https://doi.org/10.1080/14786419.2019.1698574

Tarasuntisuk S, Patipong T, Hibino T, Waditee-Sirisattha R, Kageyama H (2018) Inhibitory effects of mycosporine-2-glycine isolated from a halotolerant cyanobacterium on protein glycation and collagenase activity. *Lett Appl Microbiol* **67**: 314–320. https://doi.org/10.1111/lam.13041

Tominaga K, Hongo N, Fujishita M, Takahashi Y, Adachi Y (2017) Protective effects of astaxanthin on skin deterioration. *J Clin Biochem Nutr* **61**: 33–39. https://doi.org/10.3164/jcbn.17-35

Tomova I, Lazarkevich I, Tomova A, Kambourova M, Vasileva-Tonkova E (2013) Diversity and biosynthetic potential of culturable aerobic heterotrophic bacteria isolated from Magura Cave, Bulgaria. *IJS* **42**: 65–76. https://doi.org/10.5038/1827-806X.42.1.8

Trendowski M, Mitchell JM, Corsette CM, Acquafondata C, Fondy TP (2015) Chemotherapy with cytochalasin congeners *in vitro* and *in vivo* against murine models. *Invest New Drugs* **33**: 290–299. https://doi.org/10.1007/s10637-014-0203-5

Tribelli PM, Solar Venero EC, Ricardi MM, Gómez-Lozano M, Raiger Iustman LJ, Molin S, López NI (2015) Novel essential role of ethanol oxidation genes at low temperature revealed by transcriptome analysis in the Antarctic bacterium *Pseudomonas extremaustralis*. *PLoS One* **10**: e0145353. https://doi.org/10.1371/journal.pone.0145353

Tumbarski Y, Deseva I, Mihaylova D, Stoyanova M, Krastev L, Nikolova R, Yanakieva V, Ivanov I (2018) Isolation, characterization and amino acid composition of a bacteriocin produced by *Bacillus methylotrophicus* strain BM47. *Food Technol Biotechnol* **56**: 546–552. https://doi.org/10.17113/ftb.56.04.18.5905

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

Varshney P, Mikulic P, Vonshak A, Beardall J, Wangikar PP (2015) Extremophilic micro-algae and their potential contribution in biotechnology. *Bioresour Technol* **184**: 363–372. https://doi.org/10.1016/j.biortech.2014.11.040

Voytsekhovskaya IV, Axenov-Gribanov DV, Murzina SA, Pekkoeva SN, Protasov ES, Gamaiunov SV, Timofeyev MA (2018) Estimation of antimicrobial activities and fatty acid composition of actinobacteria isolated from water surface of underground lakes from Badzheyskaya and Okhotnichya caves in Siberia. *PeerJ* **6**: e5832. https://doi.org/10.7717/peerj.5832

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 sphaerospermum*. *J Nat Prod* **77**: 270–275. https://doi.org/10.1021/np400833x

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

Yoshihisa 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

Yücel S, Yamaç M (2010) Selection of *Streptomyces* isolates from Turkish karstic caves against antibiotic resistant microorganisms. *Pak J Pharm Sci* **23**: 1–6

Zhang Z, Li S, Li J, Gu X, Lin X (2019) Complete genome sequences of a H_2O_2-resistant psychrophilic bacterium *Colwellia* sp. Arc7-D isolated from Arctic Ocean sediment. *Marine Genomics* **43**: 65–67. https://doi.org/10.1016/j.margen.2018.08.001

Zhou X, Fang W, Tan S, Lin X, Xun T, Yang B, Liu S, Liu Y (2016) Aspernigrins with anti-HIV-1 activities from the marine-derived fungus *Aspergillus niger* SCSIO Jcsw6F30. *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) Furanone derivative and sesquiterpene from Antarctic marine-derived fungus *Penicillium* sp. S-1-18. *J Asian Nat Prod Res* **20**: 1108–1115. https://doi.org/10.1080/10286020.2017.1385604

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