



Terrestrial Extremophiles as a Potential Source of Novel Antibiotics to Combat Multi-Drug Resistant Pathogens

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Abstract

Human and animal health are increasingly affected by multidrug-resistant pathogens despite efforts to address the challenge. Research focus shifted to microorganisms from extreme environments as possible sources of antibiotics and metabolites to halt the menace of resistance in pathogens. This paper explores the rich collection of metabolites produced by these microorganisms, their environment, and their applications. Given their intricate nature, these organisms may harbor mechanisms for producing novel metabolites and antibiotics to combat multidrug-resistant pathogens. We highlight recent advances in the isolation, screening, and characterization of antibiotic-producing extremophiles from their harsh terrestrial environments. Studying the diverse chemical scaffolds and mechanisms of action in these microbes can inform the development of effective antimicrobials. Furthermore, we discuss the challenges and prospects of harnessing the vast array of terrestrial microorganisms in extreme environments to combat antibiotic resistance.

Keywords: Resistant pathogens, terrestrial, extremophiles, metabolites, antibiotics

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Introduction

Antibiotic resistance and the global health crisis

Infectious diseases have long threatened human survival, and recent deadly outbreaks demand more pragmatic measures to curb their spread. The burden of infectious diseases globally is exacerbated by antibiotic resistance, which undermines effective treatment options. Antibiotic resistance is a global health crisis driven by the misuse of antibiotics, the emergence of resistant microorganisms, and the spread of resistance genes [1]. Antibiotics kill or inhibit bacterial growth; however, misuse through wrong prescription, failure in completing the full course, or inappropriate use in agriculture and livestock production has led to antibiotic resistance. Due to their innate ability to adapt, bacteria, when exposed to antibiotics, may develop resistance characteristics that enable them withstand the drug's effects [2, 3]. They can subsequently multiply and spread to cause infections that are difficult to treat. Antibiotic resistance has a multifaceted effect on health, including increased treatment failures and mortality. The increasing morbidity and mortality rates both place a heavy burden on healthcare institutions [4]. Antibiotic resistance reduces treatment options when infections become complicated, leaving healthcare facilities with limited or no effective treatment options. This scenario puts patients' lives at risk and frustrates the

management of such infections. Healthcare-associated infections (HAIs) caused by resistant pathogens are problematic as they affect vulnerable populations, prolong hospital stays, and increase treatment costs. Antibiotic resistance also impacts productivity among sick people and does not respect borders. They spread within communities and across countries through travel, trade, and migratory routes, making it difficult to contain and control the spread of infection [5].

Seeking new solutions: Microorganisms from extreme terrestrial habitats

Certain habitats are considered very difficult to inhabit due to the extreme conditions they present. Extremophiles grow optimally in these extreme or harsh habitats for life. Examples of these environments include arid deserts, volcanoes, deep ocean trenches, the Arctic and Antarctic poles, the upper atmosphere, and outer space, among others. Such environments lie outside the temperature range of 10-37 °C, the salinity range of 0.15 to 0.5 NaCl, atmospheric pressure of 1 atm, and a pH of ~7, where life forms are supported [6]. Organisms living in these environments are often well adapted to the conditions of these environments, and their survival strategies are typically shaped by long-term evolutionary changes [7]. These organisms have been carefully studied over time because they defy



biochemical and metabolic attributes under which organisms are expected to grow and survive. They are target organisms for evolutionary studies because of their characteristic adaptations shaped over the years.

The diversity of terrestrial microorganisms

Prokaryotes were the dominant group in Earth's evolutionary history. They evolved and occupy all available niches. Extremophiles are found across the three domains of life. These mutants survive in harsh environments and synthesize macromolecules (lipids, enzymes, nucleic acids) that are tolerant of such extremes. Some thrive in extreme temperature environments (thermophiles and hyperthermophiles), and others are adapted to low temperature environments (psychrophiles). Acidophiles thrive in acidic environments, and alkalophiles inhabit alkaline habitats, while barophiles grow in high pressure environments.

Microbial Communities in Extreme Terrestrial Environments

Microbial communities in extreme terrestrial environments thrive under inhospitable conditions. Examples of such extreme environments are highlighted below (Fig. 1);

- a) Thermophiles:** Microorganisms are metabolically active across a temperature range from -20 to 122 °C. Extremophiles are active between 41 and 122 °C. These microbes are mostly anaerobic, either chemo-heterotrophs or chemo-lithoautotrophs capable of surviving by metabolizing hydrothermal energy sources [8]. These microorganisms are found in hot natural ecosystems, including geothermal waters, hot springs, geysers, volcanoes, fumaroles, mud pots, and deep-sea hydrothermal vents. Hyperthermophiles are thermophiles that are active at temperatures >80 °C. Hyperthermophiles belong to the domain Archaea, making them one of the earliest life forms on Earth. However, a few bacteria can withstand fluid temperatures of approximately 100 °C. Fluid temperatures exceeding 100 °C are observed when hydrothermal or magmatic activity coincides with high pressure, as in deep-sea hydrothermal vents and deep subsurface environments near volcanoes [9]. Thermophilic bacteria from ocean depths are piezo-tolerant (most are piezophilic) and halotolerant. Examples include *Thermococcus* spp., *Pyrococcus* spp., and *M. kandleri* [10]. *Geotoga* and *Petrogoga* are extreme thermophiles commonly found in deep subsurface oil reservoirs.
- b) Acidophiles:** Acidophiles survive in volcanic vents, acidic sulfur springs, and acid mine drainage sites (optimal pH <5), which are characterized by heavy-metal deposits. These microorganisms grow

at neutral pH and acquire resistance to some metals [11]. Acidophiles are distributed across the Archaea, bacteria, and eukarya domains. They are usually members of the genera *Acidobacterium*, *Leptospirillum*, *Picrophilus*, and *Ferroplasma* [12].

- c) Psychrophiles (Cryophiles):** This group of organisms grows and reproduces within the temperature range of -20 to +10 °C [13]. An example is the ultra-cold, freezing point in East Antarctica. Numerous studies on psychrophiles in the Antarctic region have identified bacteria belonging to the taxa Actinobacteria, Alphaproteobacteria, Betaproteobacteria, Chlorobi, Chloroflexi, Cyanobacteria, Deltaproteobacteria, Firmicutes, Gammaproteobacteria, Bacteroidetes, Planctomycetes, Spirochaetes, and Verrucomicrobia [14]. These organisms are unique, in that they produce antifreeze proteins that help them cope with freezing temperatures.
- d) Alkaliphiles:** Alkaliphiles thrive in alkaline environments where pH ranges 8.5 to 11, with an optimal pH of 10 [6]. Obligate alkaliphiles such as *Bacillus krulwichiae*, can survive at a high pH range 10 to 12, while facultative alkaliphiles thrive better from pH 7 to 9.5 normal environmental conditions. Halo-alkaliphiles are microorganisms which require high salt concentrations to survive.
- e) Halophiles:** Halophiles are high-salt loving microbes that require salt to grow. This group of obligate extremophiles are classified into slight halophiles (0.2 M NaCl concentration), moderate halophiles (0.5-2.5 M NaCl), borderline extreme halophiles (>2.0-4.0 M NaCl), and extreme halophiles (>4.0-5.9 M NaCl) [15]. Saline habitats such as soda lakes (37.1 % salt concentration), hot springs (about 15 % salinity), and salt inclusions (up to 49.7 % salinity) are common in marine environments. Bacterial strain *Halarsenatibactersilvermanii* was isolated from an alkaline hypersaline lake (35 % NaCl concentration), Searle's Lake, USA.
- f) Barophiles:** Barophiles thrive in high-pressure environments found on the ocean floors and in deep lakes, at pressures \geq 380 atm. *Thermococcus piezophilus*, a thermophile is capable of growing at 125 MPa. Phylogenetic studies placed some barophilic bacteria in the genus *Shewanella*, known as the barophilic branch [16]. This subgroup of microorganisms survives in cold, dark, low-nutrient, high-pressure environments. They possess characteristic pressure-regulated genes, which are not yet fully characterized. Their applications range from deep-sea waste disposal to the provision of biocatalysts for high-pressure bioreactors [16].

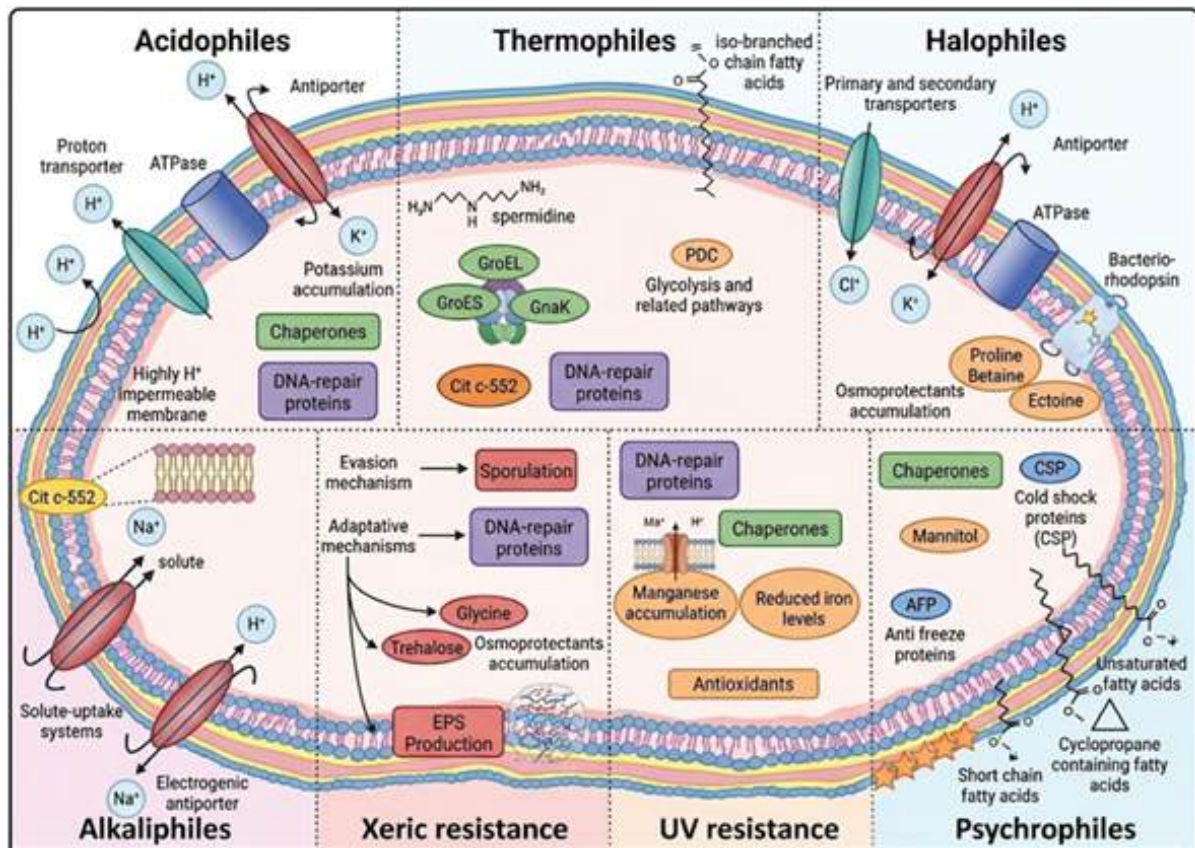


Figure 1: Microbial communities in extreme terrestrial environments (Figure adapted from Orellana et al. [6])

Harnessing terrestrial biodiversity

Harnessing the microbial diversity in the soil environment involves exploring the diverse groups of microorganisms present there. Microorganisms are the most abundant and diverse, and they play crucial roles in ecological processes. These organisms have applications in agriculture, biotechnology, medicine, and remediation.

Isolation and Screening Strategies

Isolation and identification of microorganisms are important for characterising them as novel and for identifying their peculiar traits or capabilities. The strategies commonly employed in the isolation and screening of these microbes could be cultivation or non-cultivation-based approaches (Figs 2 and 3).

Cultivation-based approaches

Cultivation of microorganisms is used to isolate and identify microorganisms from soil. This system is limited because some microbes cannot be cultured using the traditional laboratory techniques. The strategy remains valuable and easily available for accessing the cultivable fraction of microbes in the environment. Cultivation approaches follow these general steps (Fig. 2);

- i. **Sample collection:** Sampling can be from different environments, and samples should be collected aseptically. They should be stored

under appropriate conditions to preserve the viability of organisms.

- ii. **Dilution and plating:** Serial dilution of the sample is performed to reduce the microbial load from the samples. Aliquots from the diluted sample are spread or streaked onto various selective or general-purpose solid culture media to obtain the microorganisms present in the sample. Different media compositions and selective agents allow for the isolation of particular microbial groups and or organisms with specific functional traits.
- iii. **Incubation:** Incubation is done at a specific temperature, which should be close to the temperature of the environment where the organism is resident. Incubation for microbial growth should factor in pH and oxygen levels of the growth medium.
- iv. **Colony morphology and pure culture isolation:** After incubation, colonies with distinct morphologies are sub-cultured and selected for further characterization. Single colonies are transferred to fresh media to obtain pure cultures.
- v. **Phenotypic and genotypic characterization:** Isolates are characterized to know their growth characteristics, biochemical properties, and physiological traits. The information obtained helps to preliminarily group or classify isolated microorganisms. Genotypic characterization



such as DNA sequencing and fingerprinting methods is employed to confirm the identity of a microorganism, determine their genetic diversity and relatedness among the isolated strains [17].

- vi. **Screening for desired traits:** Isolated strains can be screened for traits of interest. These characteristics in microorganisms could confer advantages in enzymatic capabilities, bioactive compound production, or tolerance to

environmental stressors. Screening can be performed *in vitro* or *in vivo*, depending on the desired trait.

- vii. **Preservation and further studies:** Isolated strains with desirable characteristics can be preserved using cryopreservation or lyophilization to ensure long-term storage and availability for further studies and applications.

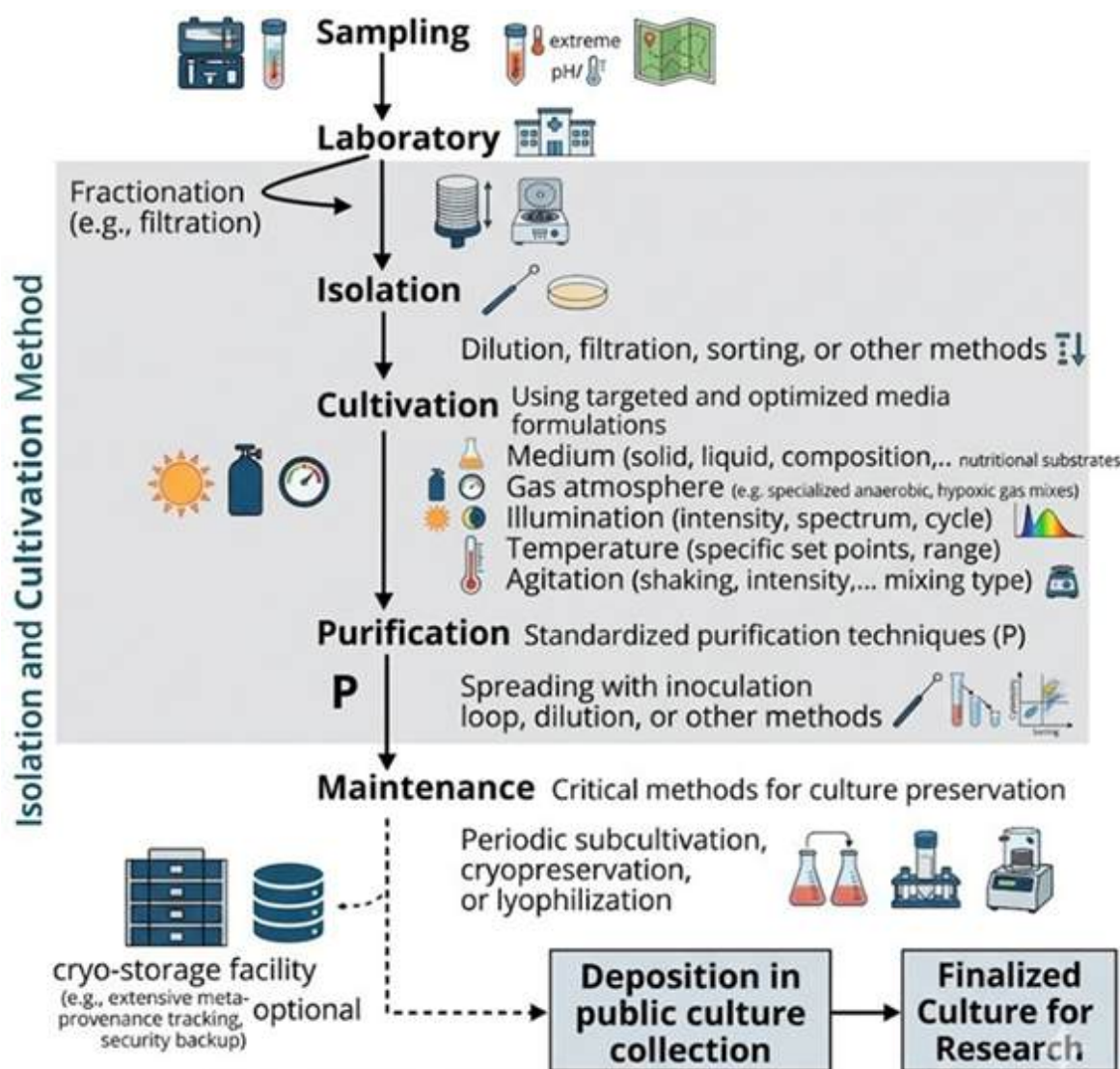


Figure 2: Cultivation-based approach to Isolation and screening for Bioactive Extremophiles

Cultivation to isolate microorganisms is limited because the procedure only covers a small fraction of the microbial population, a phenomenon known as the “great plate count anomaly.” To overcome this limitation, complementary cultivation adopting independent techniques, like metagenomics and single-cell genomics, can be employed to study the uncultured microbial majority and access their genetic information [18].

Non-cultivation methods: Metagenomics and metabolomics

Metagenomics, metabolomics and other omic techniques have revolutionized microbial studies [19]. Metagenomics is the extraction and sequencing of DNA from environmental samples. It enables the study of genomes of microbial communities and to access the genetic information in uncultured microorganisms. Environmental samples like soil, water, or other habitats are processed to extract total DNA from the

samples, followed by DNA extraction and purification. High-quality DNA is needed for the downstream metagenomic analyses.

The extracted DNA is sequenced to obtain a large volume of data from the microbial community. These are then analyzed using bioinformatic tools to reconstruct and characterize the genomes and genes of microorganisms present in the sample. This enables the identification of functional genes and metabolic pathways of the microorganisms in the community. Metagenomic data can be functionally annotated to predict what the identified genes encode, thus providing metabolic and functional insights of the microbial community.

Metabolomics is the study of small molecules, or metabolites, produced by living organisms. It is a comprehensive profiling of metabolites in a biological sample. Metabolomics involves the collection of samples (microbial cultures, environmental matrices, or

host-associated tissues) from which metabolites are extracted. The extraction protocol is dependent on the nature of the metabolites and the sample matrix. The extracted metabolites are analyzed with mass spectrometry (MS) or nuclear magnetic resonance (NMR) spectroscopy to generate profiles of metabolites present in the sample. The obtained metabolomics data are processed and analyzed using statistical and bioinformatic tools. Metabolite identification and quantification are achieved by comparing the experimental data with metabolite databases. The data are integrated with other omics data, from which inferences about the metabolic pathways and functional characteristics of microorganisms are drawn. This integration can help identify metabolic signatures, signalling pathways that determine interactions, and the presence of biomarkers [20].

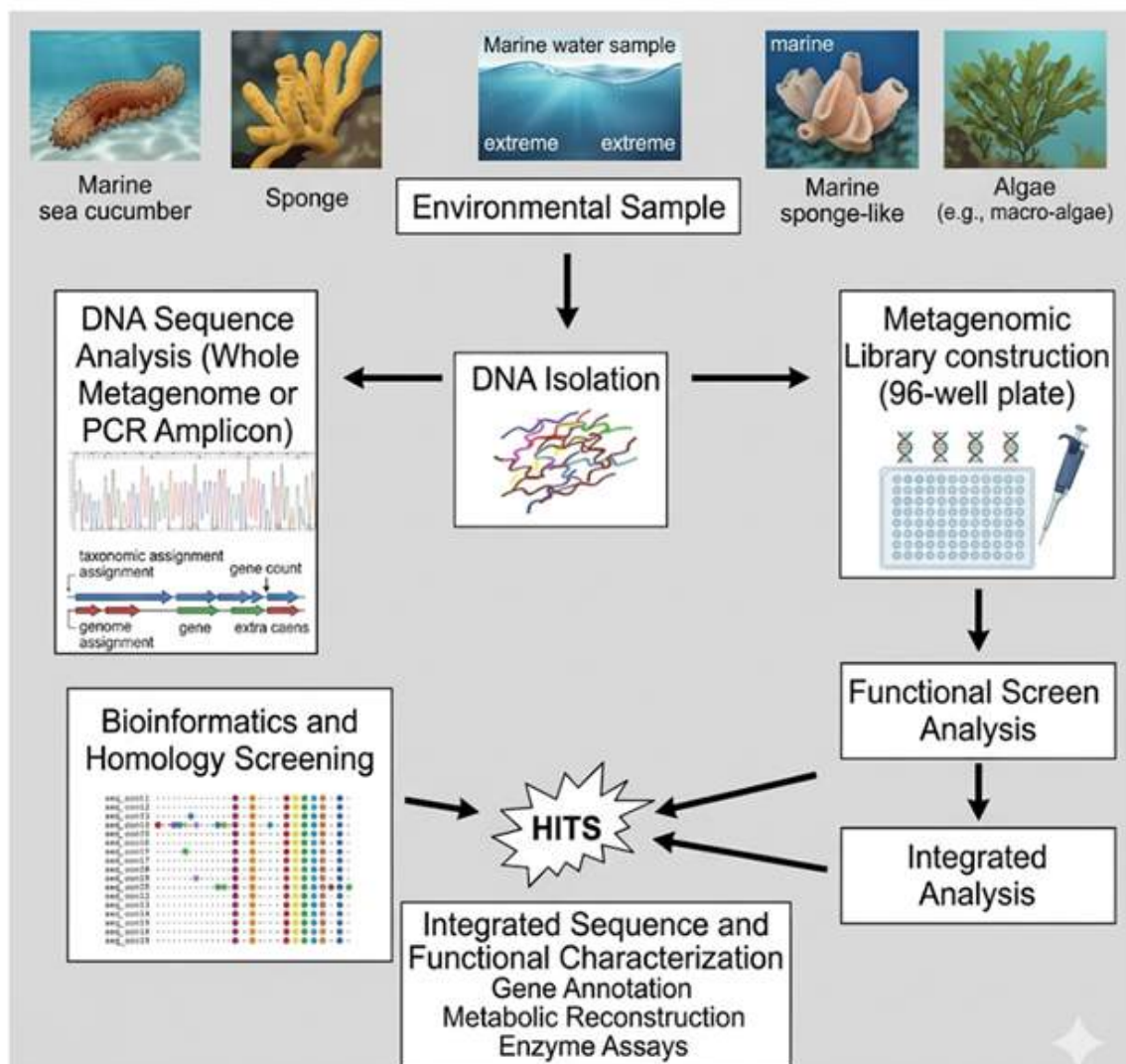


Figure 3: Non-cultivation-based approach to Isolation and screening for Extremophilic Natural Products



Metabolomics is also used for the characterization of the different chemicals and metabolic products present in microbial communities. Its application has helped in the discovery of new bioactive compounds and a better understanding of microbial interactions. Both metagenomics and metabolomics provide approaches to study the microbial communities with their diversity and function without cultivation. By combining these non-cultivation methods with the cultivation methods, a more comprehensive understanding of the microbial communities can be achieved.

Antibiotics derived from terrestrial extremophiles

Antibiotics produced by extremophiles are promising, and they often have antimicrobial potential. The production of metabolites by extremophiles is a survival strategy of adapting to the harsh environment, and is made possible through the evolution of the microorganisms over the years [21]. Exploring extremophiles for antibiotic discovery could lead to new compounds and mechanisms of action against resistant bacteria. A few examples of antibiotics derived from extremophiles are;

- a. ***Geomicrobium* sp. EMB2** is a bacterium isolated from a deep-sea hydrothermal vent. It produces Abyssomicin C, an antibacterial compound that demonstrated activity against methicillin-resistant *Staphylococcus aureus* (MRSA) [22].
- b. ***Streptomyces* sp.:** *Streptomyces* are soil bacteria. They produce a wide range of antibiotics, including streptomycin, tetracycline, and erythromycin. Many *Streptomyces* tolerate extreme temperatures or high salinity environments [23].
- c. ***Salinospora tropica*** is an actinomycete found in marine sediments. Although it is not strictly a terrestrial extremophile, it thrives in highly saline environments. The bacteria produce salinosporamide A, a potent antibiotic active against drug-resistant bacteria. It is currently being studied for its activity in the treatment of multiple myeloma [22].
- d. **Thermophilic bacteria:** These bacteria are rich sources of antibiotics. They also secrete important metabolites and compounds of industrial importance. *Thermus aquaticus*, for example, produces *Taq* polymerase, an enzyme readily used in the polymerase chain reaction (PCR).

Chemicals and novel compounds produced by extremophiles

Extremophiles are rich sources of compounds with a wide range of applications (Table 1, Fig. 5). Their survival led to evolution with unique metabolic pathways, which resulted in the production of compounds with remarkable chemical activities [24]. Examples are:

Polyextremophilic compounds are extremophiles that tolerate multiple extreme conditions to produce compounds known as polyextremophilic compounds. These molecules possess chemical structures and properties that enable them to function under different extreme conditions. An example is extremozyme that remains active and stable at high temperatures and in acidic environments [24].

Thermophilic enzymes: Extremophiles adapted to high-temperature environments produce enzymes with exceptional stability and activity at high temperatures. These enzymes, known as thermozymes, have applications in biofuel production, food processing, and DNA amplification (PCR). Thermozymes offer advantages over conventional enzymes due to their stability at high temperatures, which improves efficiency and reduces risk of contamination [25].

Halophilic compounds: Halophiles produce pigments that have applications in food coloring and pharmaceuticals. The pigment enables their survival in saline environments.

Acidophilic compounds: Acidophilic compounds function and remain stable under acidic conditions. These compounds have industrial applications in the development of acid-resistant materials and in bioremediation processes to clean up acidic waste sites.

Alkaliphilic compounds: Alkaliphiles produce compounds with applications in the manufacture of detergents and in the development of alkaline-stable catalysts.

Psychrophilic compounds: Psychrophiles produce compounds with chemical structures and properties adapted to low temperatures. These compounds have potential applications in food preservation, cryopreservation, and biomedical research.

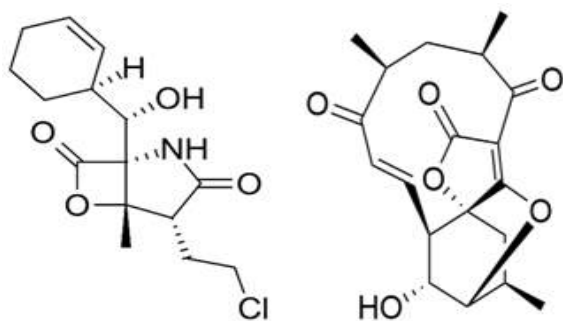


Figure 4: Salinosporamide A and abyssomicin C.

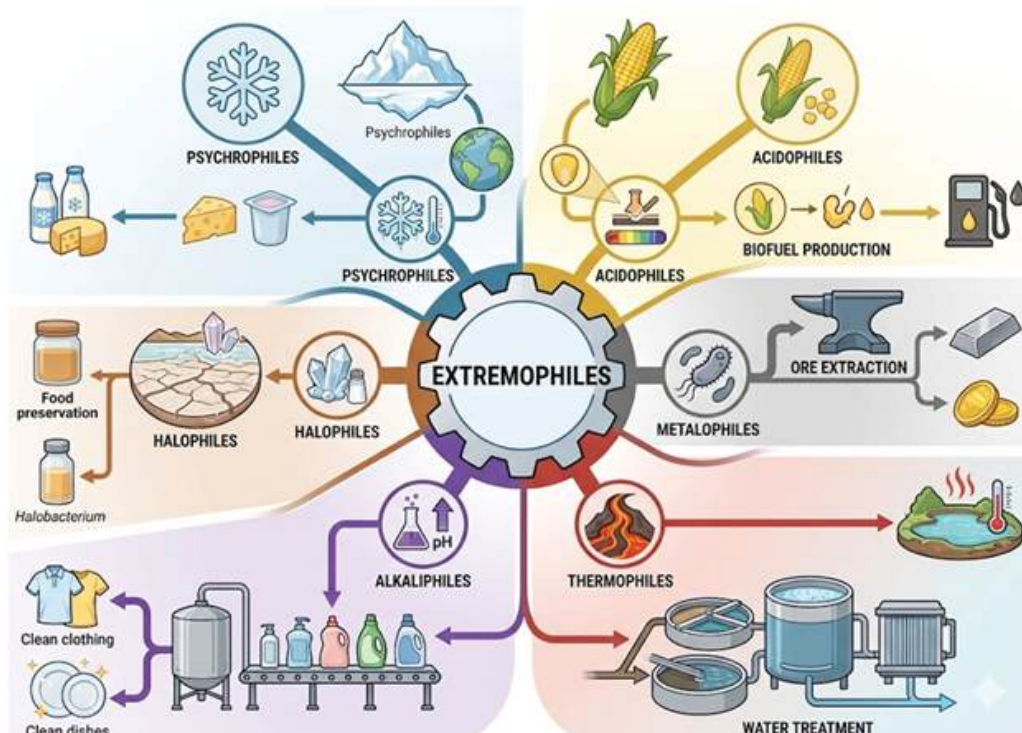


Figure 5: Application of novel compounds from extremophiles

Table 1: Some examples of compounds produced by extremophiles and their applications

Compound	Chemical Class	Producer Organism	Extremophile Type	Extreme Environment	Significance	Ref.
Thermorubin	Polyketide antibiotic	<i>Thermoactinomycesantibioticus</i>	Thermophile	Hot soils, high-temperature habitats	Ribosome-targeting antibiotic	
Salinosporamide A	Proteasome inhibitor	<i>Salinispora tropica</i>	Marine halophile	Deep-sea marine sediments	Anticancer drug lead	[26]
Halocin	Protein antimicrobial	<i>Haloferaxmediterranei</i>	Halophile	Salt lakes	Antimicrobial activity	[27]
Ectoine	Extremolyte (osmoprotectant)	<i>Halomonas elongata</i>	Halophile	Hypersaline environments	Stress protection, cosmetics	[28]
Trehalose	Protective disaccharide	<i>Deinococcusradiodurans</i>	Radiophile	Radiation-exposed habitats	Cellular stress protection	
Taq Polymerase	Thermostable enzyme	<i>Thermus aquaticus</i>	Thermophile	Hot springs	PCR, molecular diagnostics	[29]
Cold-Active Lipases	Enzyme	<i>Psychrobacter</i> spp.	Psychrophile	Polar regions	Detergents, bioremediation	[30]
Bacteriorhodopsin	Light-driven proton pump (retinal binding protein)	<i>Halobacterium salinarum</i>	Halophile	Salt flats	Bioelectronics, optical memory	[31]
Antifreeze Proteins	Cryoprotectant proteins	<i>Colwelliapsychrerythraea</i>	Psychrophile	Arctic seawater	Cryopreservation	[32]
Carotenoids	Antioxidant pigments	<i>Deinococcusradiodurans</i>	Radiophile	High-radiation environments	UV protection, nutraceuticals, antioxidants	[33]
Thermophilic Amylases	Enzyme	<i>Geobacillus stearothermophilus</i>	Thermophile	Geothermal soils	Industrial starch processing	[34]
Siderophores	Iron-chelating compounds	<i>Acidithiobacillusferrooxidans</i>	Acidophile	Acid mine drainage	Bioremediation, mining	[35]
Methanogenic Cofactors	Unique coenzymes	<i>Methanopyruskandleri</i>	Hyperthermophile	Hydrothermal vents	Bioenergy, methane metabolism	
Mannosylglycerate PHAs (Bioplastics)	Compatible solute Biopolymer	<i>Thermococcus litoralis</i> <i>Haloferaxvolcanii</i>	Hyperthermophile Halophile	Deep-sea vents Hypersaline waters	Protein stabilization Biodegradable plastics	[36] [37]
Cold-Shock Proteins	Stress-response protein	<i>Psychromonasingrahamii</i>	Psychrophile	Antarctic ice	Cryobiology applications	
Biosurfactants	Glycolipids	<i>Rhodococcus</i> spp.	Extremotolerant	Oil-contaminated extreme soils	Oil spill remediation	[38]
Exopolysaccharides (EPS)	Biopolymer	<i>Halomonasmaura</i>	Halophile	Saline waters	Food, pharmaceutical stabilizers	[39]
Alkaline Proteases	Industrial enzyme	<i>Bacillus halodurans</i>	Alkaliphile	Soda lakes	Detergent and leather industries	[40]
Melanin	Protective pigment	Radiation-resistant fungi (e.g., <i>Cryptococcus</i> spp.)	Extremotolerant	Radiation-rich environments	UV shielding, medical research	[41]

**Table 2: Ribosome targeting antibiotics derived from extremophile**

Antibiotic	Source/Environment	Producing Organism	Ribosomal Target	Mechanism of Action
Thermorubin	Thermophilic (high-temperature environments)	<i>Thermoactinomycesantibioticus</i>	50S subunit	Inhibits peptide bond formation by blocking the ribosomal A-site
Erythromycin	Extreme soil / stress-tolerant actinomycetes	<i>Saccharopolyspora erythraea</i>	50S subunit	Blocks nascent peptide exit tunnel, stopping elongation
Streptomycin	Harsh soil / environmental extremotolerant microbes	<i>Streptomyces griseus</i>	30S subunit	Causes misreading of mRNA and inhibits initiation
Tetracycline	Saline/arid soil extremophiles	<i>Streptomyces aureofaciens</i>	30S subunit	Prevents aminoacyl-tRNA binding to the A-site
Chloramphenicol	Environmentally resilient microbes	<i>Streptomyces venezuelae</i>	50S subunit	Inhibits the peptidyl transferase enzyme
Gentamicin	Stress-tolerant soil bacteria	<i>Micromonospora purpurea</i>	30S subunit	Causes mRNA misreading and defective protein synthesis
Kanamycin	Extreme soil actinomycetes	<i>Streptomyces kanamyceticus</i>	30S subunit	Disrupts translational accuracy and initiation
Puromycin	Extreme soil microbes	<i>Streptomyces alboniger</i>	50S subunit	Causes premature chain termination
Linezolid(<i>synthetic, bio-inspired</i>)	Modeled on microbial ribosome-binding scaffolds	Synthetic (inspired by actinomycetes)	50S subunit	Prevents the formation of the initiation complex
Spectinomycin	Harsh environmental bacteria	<i>Streptomyces spectabilis</i>	30S subunit	Inhibits ribosomal translocation
Hygromycin B	Extreme soil actinomycetes	<i>Streptomyces hygrosopicus</i>	30S subunit	Causes ribosomal decoding errors
Salinosporamide-related ribosome inhibitors	Marine extremophile	<i>Salinispora tropica</i>	Ribosome-associated pathways	Disrupts protein synthesis regulation

Mechanisms of Action

Extremophiles synthesize metabolites that exhibit distinct mechanisms of action compared with those from other sources. The specific mechanisms of action of antibiotics derived from extremophiles can vary across compounds. However, here are some common mechanisms:

Disruption of cell wall synthesis: Some antibiotics derived from extremophiles interfere with cell wall synthesis in bacteria. They inhibit the activity of enzymes involved in peptidoglycan synthesis, and weaken the cell wall, which leads to cell lysis and bacterial death. A typical example of an antibiotic that adapts this mechanism is Teixobactin, a recently discovered antibiotic derived from soil bacteria. It was isolated from an unculturable bacterium found in a grassy field soil sample.

Inhibition of protein synthesis: Some antibiotics target the bacterial ribosomes to prevent protein synthesis. These antibiotics bind to specific sites on the ribosome and interfere with translation, thereby inhibiting protein synthesis in bacteria. Disruption of protein synthesis prevents the production of essential proteins, leading to bacterial death [23]. GE2270A, an antibiotic produced by *Planobispora rosea*, inhibit protein synthesis by binding to the 50S subunit of the bacterial ribosome, which prevents peptide bond formation during translation. This binding disrupts protein synthesis and ultimately leads to bacterial cell death [42].

Disruption of bacterial DNA replication: Some antibiotics interfere with the replication of bacterial DNA. This group of antibiotics targets enzymes involved in DNA replication, such as DNA gyrase and topoisomerase, which are necessary for DNA unwinding and replication [22]. By inhibiting these enzymes, they prevent proper replication of DNA. Salinosporamide A, also known as NPI-0052 or

marizomib, is an antibiotic and proteasome inhibitor produced by the extremophilic bacterium *Salinispora tropica*. It binds to and inhibits the activity of the 20S proteasome, an enzyme complex involved in protein degradation. The disruption of protein degradation machinery interferes with DNA replication and cell cycle progression in bacteria [22].

Membrane disruption: Extremophiles also produce antibiotics that can disrupt the bacterial cell membrane. They target specific components of the membrane, such as phospholipids or membrane proteins, thereby altering permeability and compromising cellular integrity [43]. This disruption can cause leakage of cellular contents and ultimately result in bacterial death. Daptomycin, produced by *Saccharopolyspora hirsutais* an antibiotic that mimics the properties of a peptide in the bacterial cell membrane. Daptomycin can get inserted into the bacterial cell membrane to depolarize and disrupt the membrane functioning. This leads to the leakage of intracellular ions causing bacterial cell death [43].

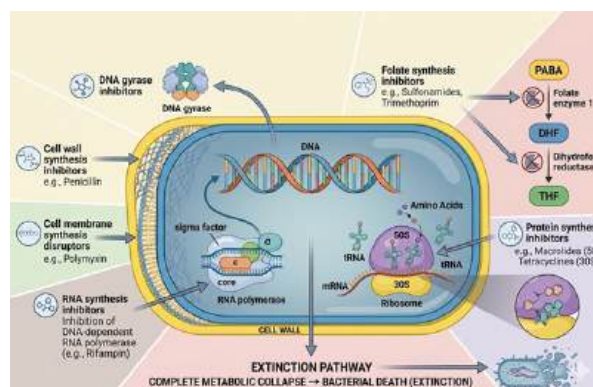


Figure 6: Mechanism of action of antibiotics from extremophiles



Overcoming Challenges in Antibiotic Discovery

Antibiotic discovery faces several challenges that must be addressed to combat the growing problem of antibiotic resistance and ensure a sustainable pipeline of new antibiotics. Some of the key challenges include:

Antibiotic resistance: The emergence and spread of antibiotic-resistant bacteria pose a significant challenge for antibiotic discovery. Bacteria can acquire resistance through genetic mutations or by acquiring resistance genes from other bacteria. To overcome this challenge, innovative approaches are needed to identify and develop antibiotics that circumvent existing mechanisms of resistance.

Declining productivity of traditional screening methods: Traditional methods of screening for antibiotics, such as cultivating microorganisms from soil samples, yielded many of the antibiotics we currently use. However, the rate of discovery of novel antibiotics using these methods has declined significantly. New screening techniques and technologies, such as metagenomics and high-throughput screening, are being explored to enhance the discovery process.

Access to diverse microbial sources: The majority of known antibiotics were derived from a small number of microbial species. Accessing diverse microbial sources, including extremophiles and uncultivable bacteria, is crucial to discovering novel antibiotics with unique mechanisms of action. Developing culture methods for previously uncultured microorganisms and exploring alternative sources, such as marine environments, are important for expanding the pool of potential antibiotic-producing organisms.

Discovery of new targets and mechanisms of action: Identifying new targets in bacterial pathogens and understanding their underlying biology is essential for developing effective antibiotics. In addition, discovering antibiotics with novel mechanisms of action can help overcome existing resistance mechanisms. Advancements in genomics, proteomics, and other omics technologies are aiding in the discovery of new targets and facilitating the understanding of bacterial physiology.

Optimization and development of antibiotic candidates: Once a potential antibiotic is identified, it often requires optimization to enhance its efficacy, improve pharmacokinetic properties, and minimize toxicity. This process involves medicinal chemistry and formulation techniques to optimize the drug candidate for clinical use. Developing strategies to streamline and accelerate the optimization process is crucial for bringing new antibiotics to market [44].

Economic and regulatory challenges: Antibiotic development is a complex and costly process. The return on investment for developing new antibiotics is often low due to factors such as limited treatment duration, the risk of resistance development, and low market demand. Addressing these challenges and implementing policies that incentivize antibiotic research and development are necessary to attract

investment and ensure the sustainability of antibiotic discovery efforts.

Overcoming Cultivation Challenges

Cultivation challenges in antibiotic discovery are the difficulties encountered in cultivating and isolating microorganisms that produce antibiotics. Many microorganisms, particularly those capable of producing novel antibiotics, are difficult to culture in the laboratory. Overcoming these challenges is crucial for accessing the vast microbial diversity and unlocking their antibiotic-producing potential. Here are some strategies to address cultivation challenges:

Alternative culture conditions: Microorganisms often have specific growth requirements that are not easily replicated in standard laboratory conditions. By modifying culture media, temperature, pH, oxygen levels, and other environmental factors, it is possible to create conditions that more closely mimic the target microorganism's natural habitat. This approach, known as "bioprospecting under ecologically relevant conditions", can increase the likelihood of successful cultivation [45].

Co-culturing and coculture-dependent approaches: Many microorganisms have complex interactions with other organisms in their natural environment. Co-culturing techniques involve growing microorganisms in the presence of other organisms, such as neighboring bacteria or fungi, to recreate these interactions. Co-culturing can stimulate the expression of silent or cryptic biosynthetic gene clusters responsible for antibiotic production. Similarly, coculture-dependent approaches exploit interactions among multiple microorganisms to induce antibiotic production [45].

Microfluidics and single-cell techniques: Microfluidics platforms provide a controlled and dynamic environment for the growth of microorganisms. These systems enable precise manipulation of culture conditions, including nutrient gradients, spatial organization, and interactions with other microorganisms. Single-cell techniques, such as single-cell genomics and transcriptomics, can be used to analyze the metabolic potential of individual microorganisms, including those that are difficult to cultivate.

High-throughput screening of uncultivable microorganisms: Advances in metagenomic sequencing technologies have made it possible to study the genetic material of uncultivable microorganisms directly from environmental samples. By analyzing the DNA or RNA extracted from these samples, researchers can identify biosynthetic gene clusters responsible for antibiotic production. This information can inform the design of synthetic biology approaches or heterologous expression systems for producing antibiotics.

Synthetic biology and genetic engineering: Synthetic biology approaches involve the engineering of microorganisms to produce desired compounds. By leveraging genetic information from uncultivable



microorganisms, it is possible to transfer biosynthetic gene clusters into genetically tractable hosts, such as model bacteria or fungi, for expression and production of the desired antibiotic. Genetic engineering techniques can also be used to manipulate and optimize biosynthetic pathways to enhance antibiotic production.

Mining of genomic data: The vast amount of genomic data available in public databases provides a valuable resource for antibiotic discovery. By analyzing the genomes of known antibiotic producers and their related organisms, researchers can identify biosynthetic gene clusters that may be responsible for antibiotic production. This information can guide the selection of microorganisms for cultivation and screening.

Overcoming resistance mechanisms

Overcoming resistance mechanisms in pathogens is a crucial aspect of antibiotic development and of combating antibiotic resistance. Some strategies and approaches that can help overcome resistance mechanisms are highlighted below;

Combination therapy: Using a combination of antibiotics with different mechanisms of action can be an effective strategy to combat resistance. Combining two or more antibiotics can target multiple pathways in bacteria, making it harder for bacteria to develop resistance. This approach reduces the likelihood of bacteria evolving mechanisms to counteract the effects of multiple drugs simultaneously.

Targeting new bacterial vulnerabilities: Exploring and identifying novel bacterial targets that are less prone to resistance can be an effective strategy. By focusing on essential processes that are less likely to mutate or develop resistance mechanisms, researchers can design antibiotics with a lower risk of resistance emergence. Examples include targeting bacterial virulence factors, essential metabolic pathways, or non-traditional targets such as bacterial biofilms [46].

Enhancing drug delivery: Improving the delivery of antibiotics to the site of infection can enhance their efficacy and reduce the emergence of resistance. Strategies such as developing drug formulations that enhance tissue penetration, overcoming bacterial efflux pumps that expel antibiotics from bacterial cells, or using nanoparticle-based drug delivery systems can increase antibiotic concentrations and exposure at the site of infection [47].

Developing adjuvants and resistance inhibitors: Adjuvants are compounds that can be used in combination with antibiotics to enhance their efficacy or restore their effectiveness against resistant bacteria. They can act by disrupting resistance mechanisms or by enhancing antibiotic activity. Similarly, resistance inhibitors can be designed to block specific resistance mechanisms employed by bacteria, thereby increasing susceptibility to antibiotics.

Repurposing existing drugs: Screening existing drugs that are approved for other purposes can be an efficient approach to identify compounds that have antibacterial activity or can enhance the effectiveness of existing antibiotics. This strategy can accelerate the development process by leveraging drugs that have already undergone safety testing and have known pharmacokinetics.

Developing new antibiotics: Despite the challenges, there is still a need for the development of new antibiotics with unique mechanisms of action. Continued research and exploration of natural sources, such as extremophiles, uncultivable bacteria, and unexplored environments, can lead to the discovery of novel antibiotics that may overcome existing resistance mechanisms.

Combating the spread of resistance: Implementing measures to prevent the spread of resistant bacteria is crucial. This includes promoting appropriate antibiotic use, implementing infection control practices, and reducing the overuse and misuse of antibiotics in human and veterinary medicine, as well as in agriculture.

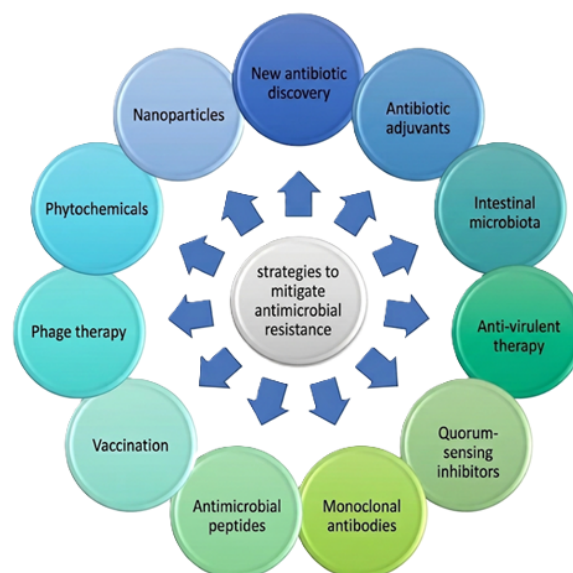


Figure 7: Current and Emerging Approaches to Combat Microbial Resistance

Overcoming resistance mechanisms requires a multifaceted approach that integrates innovative strategies, collaboration between researchers and clinicians, and robust antimicrobial practices (Fig. 7). These approaches can mitigate the development and spread of antibiotic resistance and help ensure the continued effectiveness of antibiotics in treating bacterial infections.

Conclusion

Extremophiles, which inhabit complex and harsh environments, are important communities of organisms found around Earth. The unfriendly nature of their environments has driven them to evolve to survive, a



goal shared by all living organisms. This evolution has led to the production of compounds and metabolites important to healthcare and industry by these organisms. The overuse of antibiotics and the complexity of evolution have led to pathogen resistance. Further exploration and study of extremophiles are necessary to harness this group of microorganisms. The use of biotechnology, coculturing, and other methods will go a long way toward addressing the challenge of antimicrobial resistance and toward developing new drugs for conditions such as cancer and diabetes.

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