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Unlocking nature's arsenal: A review on the isolation of novel antibacterial agents from extremophiles

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Abstract

The rising resistance of bacteria to antibiotics is a health concern that may bring us back to the pre-penicillin age. Confronted with this dilemma, the search for new sources of antibiotics has become a scientific and ethical imperative. In this respect, extremophiles have emerged as one of the most promising sources due to their ability to survive in extreme conditions and to create unique metabolic pathways. In this paper, we discuss the biochemical potential of these organisms, the most important antibacterial chemicals recovered from them and technological and research hurdles related to their isolation and pharmaceutical development. It also points to the most important contemporary research and metagenomics approaches that have opened the door to the exploration of unconventional "natural weapons" against resistant bacteria.

Keywords: Extremophiles, Antibacterial Agents, Antibiotic Resistance, Metagenomics, Natural Products, Bioprospecting.

1 Introduction

Since the mid twentieth century the world has seen a significant change in medicine, with the discovery of antibiotics, which have saved millions of lives. However, with their abuse and misuse, resistant strains of bacteria have appeared and become more common and complicated with each year [1]. Antibiotic resistance is considered the top 10 global health threat according to World Health Organization (WHO) [2]. The slow discovery rate of traditional antibiotics and the failure of many modern pharmaceutical attempts have driven scientists to turn to unconventional sources, most notably extremophiles, which thrive in thermal, chemical, and pressure conditions that are difficult to imagine as habitable environments [4].

These species are well known for their potential to synthesise bioactive secondary compounds, which are triggered by environmental stressors that induce the evolution of specialised defence and assault tools [5],[6]. This review covers the potential of these organisms, explores their antibacterial chemicals and analyses future opportunities and problems.

2 The Bio-Centric Approach

2.1 Extremophiles: Classification and Characteristics

Extremophiles are creatures capable of growth and reproduction in circumstances that are fatal to most other organisms. These conditions include temperatures above 80°C, severe pH or salinity five times greater than that of sea water [7]. Classification of environmental extremes is dependent on the type of habitat:

- Thermophiles: dwell in hot places like volcanoes.
- Halophiles: dwell in salt lakes.

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- Acidophiles and alkaliphiles: dwell in acidic or basic surroundings .
- Barophiles: dwell in the deep sea under extreme pressures.
- Radiophiles: can endure radiation e.g. *Deinococcus radiodurans*.

They have evolved very stable proteins and enzymes and are valuable in industry and medicine [8]. A comprehensive breakdown of extremophile classifications, optimal growth conditions, and representative species is provided in Table 1.

Table 1: Various categories of extremophiles, their growth characteristics and major species, adapted from Amina & Lotfi (2024)[9].

Group of extremophiles	**Growth characteristic**	**Species**
Thermophiles	High temperatures 45-70 °C	*Streptomyces mutabilis* *Thermus aquaticus,* *T. litoralis* *Thermodesulfobacterium,* *T. thermophiles,* *Staphylothermus marinus*
Psychrophiles	Low temperatures 0-25C° (optimum 15 °C)	*Cryptococcus cylindricus* *Cladosporium sp*
Halophiles	High Salinity 1-20% (w/v) (optimum at 10-12%)	*Halobacterium sp. NRC-1* *Bacillus subtilis LR-1* *Halomonas elongata*
Acidophiles	low pH 0-5 (optimum 3-5)	*Thiobacillus thiooxidans,* *Thermoplasma acidophilum,* *Thiobacillus acidophilus,* *Ferrimicrobium acidiphilum*
Alkaliphiles	High pH 9-12 (optimum around 10)	*Bacillus alcalophilus* *Bacillus circulans* *Bacillus clausii 221 (ATCC21522)*
Piezophiles	High Pressure >10 MPa	*Thermococcus barophilus* *Piezobacter thermophilus*
Xerophiles	Low water activity and high desiccation (Aw 0.7-0.9)	*Xeromyces bisporus*
Metallophiles	High metals conditions (Zn, Cd, Cu, Cr, Co, Ag, Pb, Hg…)	*Ferroplasma acidiphilum Yt* *Pseudomonas sp. W6*
Radiophiles	Intense ionizing/non-ionizing radiations (X and Gamma rays/Ultraviolet)	*Deinococcus radiophilus,* *D. radiodurans,* *Thermococcus radiotolerans*

2.2 Harsh Environments as a Catalyst for the Production of Active Compounds

The environmental stresses are so extreme that for them to survive, chemical evolution is a must. They resort to generating molecules that fight off competitors or shield themselves against physical stressors [10]. Some of these chemicals have demonstrated antibacterial efficacy against resistant bacteria such as MRSA and *Klebsiella pneumoniae* [11].

Metagenomic studies of marine sediments and seawater have identified polymyxin-resistance genes and related 'polymyxin resistome' activity within environmental microbiomes, indicating that extreme marine settings can harbor genetic determinants associated with polymyxin-like antibiotics (and thus Gram-negative antibiotic resistance) [12].

2.3 Extraction of Compounds: Modern Technologies and Methods

The main problem is that more than 90% of these organisms cannot be cultivated in the lab [13]. But the advent of metagenomics and random genetic analysis tools has created new opportunities to get genes encoding active chemicals without the necessity for culturing the entire organism [14].

Techniques for the investigation of environmental DNA (eDNA) have been successful in the identification of non-ribosomal peptide genes which are promising sources of novel antibiotics [8].

2.4 Examples of Extracted Compounds

2.4.1 Geobacillus thermoleovorans strain Ir1

It was reported to produce antimicrobial bioactive compounds with inhibition against *Staphylococcus aureus* and *Pseudomonas aeruginosa*, plus antibiofilm activity [15].

2.4.2 Halobacterium salinarum

It is isolated from salt lakes and produces an antibiotic that can break the membrane of Gram-negative bacteria [4].

2.4.3 Microbes of the Ocean Vent

Extracts of compounds from the lantibiotic family are active against the resistant bacterium *Acinetobacter baumannii* [1].

2.4.4 Bacteria from Volcanic Soil

A Streptomyces strain from Iceland was active against *Klebsiella pneumoniae* and *E. coli* [11].

3 Biological mechanisms for the production of antibacterial compounds in extremophiles

Extreme habitats are distinct biological systems, and they force microorganisms to evolve innovative chemical defence methods as a result of extreme environmental challenges such as high temperature, high salinity, acidity or radiation. Different metabolic pathways leading to the creation of antibiotic chemicals, which are typically atypical in their structural or functional composition, have been found to switch on under such extreme conditions [16].

A good example of this are thermophiles, producing heat stable peptides, able to destroy the cell walls of susceptible bacteria and halophiles, producing proteins called halocins, which retain their activity at extremely high salt concentrations, intolerable to most conventional antibiotics [17].

Most of the chemicals recovered from these species, on a molecular level, can be divided into two major groups:

- Antimicrobial peptides (AMPs) are peptides synthesised by non-ribosomal peptide synthesis routes.
- Polyketides, manufactured by large enzyme complexes known as polyketide synthases (PKSs) [18].

These processes enable extremophiles to produce molecules that have considerable structural and functional diversity, some with similar mode of action to vancomycin and polymyxin, others with completely unique chemical structures [1].

3.1 The Effect of Environmental Stresses on Stimulating Compound Production

Biosynthetic gene clusters (BGCs) are gene clusters activated by a wide range of environmental stressors such as food shortage, microbial competition and physical stress. These gene clusters are responsible for the generation of secondary metabolites and metagenomic investigations have revealed the presence of a substantial number of such in non-cultivable species [8].

Gene clusters producing new peptides with polymyxin-like action against Gram-negative bacteria have been found in an analytical analysis of deep ocean samples [11]. Other genes have been discovered to produce lipopeptides that are highly effective against *Klebsiella pneumoniae* and *Staphylococcus aureus* [1].

3.2 Cellular Mechanisms of Action of the Produced Compounds

The compounds from extremophiles have numerous modes of actions:

- Cell membrane perturbation: Many peptides bind to the phospholipids of the cell membrane resulting in the spilling of cellular contents and death of the cell [19].
- Inhibition of protein synthesis: Certain thermophilic compounds such as thermocins restrict the activity of ribosomes at high temperature and therefore hinder the growth of competing bacteria [4].
- Effect on bacterial communication systems (Quorum sensing): Chemicals produced by acid and salt-sensitive species interfere with signals of communication in bacteria thereby reducing biofilm formation [2].

3.3 The role of specific enzymes in compound stability

Special enzymes known as extremozymes (thermozymes, halozymes, etc.) are synthesised by extremophiles and preserve bioactive molecules against destruction or inactivation. These enzymes assure the activity of substances under circumstances that can surpass 90°C, or have salt concentrations higher than 20% [7].

Several of these enzymes also alter the chemical structure of substances by post-translational changes, which renders them more resistant to enzymatic breakdown and increases their stability in biological contexts [10]. These qualities have made them attractive candidates for the bioindustry to build stable antibiotics that may be employed under demanding industrial or medical circumstances .

3.4 Recent Applications of Artificial Intelligence in Mechanism Analysis

Today, AI algorithms are applied to analyse the genetic sequences of extremophiles to identify possible metabolic pathways responsible for the generation of antibiotic chemicals. Recent research has shown that machine learning models may reliably identify gene clusters that create novel chemicals without the need for organism cultivation [21]. This method allows for the discovery of hundreds of novel chemicals in species yet to be cultured.

4 Detailed Examples of Antibacterial Compounds Extracted from Extremophiles

Extremophiles have an extraordinary diversity in the biosynthesis of powerful bioactive chemicals especially antibacterial agents. Recent studies have extracted huge numbers of these chemicals from bacteria, fungi and archaea living in hot, saline or high pressure conditions. In this chapter, we will describe the most scientifically recorded instances of such substances, their mechanical properties and their major pharmacological applications.

4.1 Compounds Extracted from Thermophiles

Thermophiles are one of the most important sources of heat stable bioactive chemicals. Some strains of Thermus and Geobacillus have been demonstrated to create short peptides with a broad activity against Gram-positive and Gram-negative bacteria [22],[23].

Reported antibacterial substances from thermophilic bacteria include heat stable bacteriocins and antimicrobial peptides. Several strains of *Geobacillus stearothermophilus* produced bacteriocins that were bactericidal to closely related Geobacillus species, as well as *Bacillus cereus* and *Staphylococcus haemolyticus* . The activity was stable after exposure to temperatures up to 100°C [24]. Additionally, the Geobacillus sp. isolate ZGt-1 developed thermostable proteinaceous antimicrobials inhibiting *G. stearothermophilus*, *Bacillus subtilis* and *Salmonella Typhimurium* [22].

These peptides are characterised by great resistance to proteolytic enzymes and their capacity to retain the active spatial structure in hostile conditions. This makes them good candidates for the development of antibacterial drugs for hostile environments such as hospitals or heat-sterilized medical equipment [25].

4.2 Compounds Produced by Halophiles

Halophilic bacteria and archaea inhabit salt concentrations five times those of saltwater, and secrete characteristic materials, halocins. These proteins function in a similar way as bacteriocins, by generating holes in the bacterial cell membrane leading to leakage of the interior contents and death of the cell [17].

Halocin H6 isolated from *Haloferax mediterranei* is a good example of such, showing efficacy against several bacterial species resistant to conventional antibiotics [26],[27]. *Halobacterium salinarum* has also been shown to be capable of producing lipid compounds with antibacterial activity against Gram-positive bacteria such as *Bacillus subtilis* and *S. aureus* [28].

Halocins are characterised by their capacity to keep their activity under saline circumstances which makes them excellent for usage in the food and pharmaceutical industries, especially biosterilization of extremely saline products [17].

4.3 Compounds Derived from Barophiles and Deep-Sea Organisms

In deep-sea environments, particularly at hydrothermal vents deeper than 3,000 meters of water, host microbes create compounds with a type of antibacterial activity unmatched on the planet.

One of the most important of these compounds is Marinopyrrole A which was isolated from a marine bacterium of Streptomyces sp. in the deep Pacific Ocean and showed potent activity against Methicillin-resistant *Staphylococcus aureus* (MRSA) [29].

Salinosporamide A, which was also isolated from *Salinispora tropica*, a marine bacterium from tropical marine sediments, demonstrated antimicrobial and antitumor activity and later entered clinical trials as an anticancer agent [30],[31].

Deep environments exert tremendous pressures that result in the development of unique metabolic pathways, including highly stable enzymes, and thus increase the potential of these organisms for the discovery of new drugs [11].

4.4 Compounds Extracted from Acidophiles and Alkaliphiles

Acidophilic organisms, such as *Acidithiobacillus ferrooxidans* and *Sulfolobus solfataricus*, have been reported to produce antibacterial substances stable at low pH.

For example, acidomycin isolated from *Acidiphilium cryptum* was active against *E. coli* and *Klebsiella pneumoniae* [32].

In contrast, alkaliphilic organisms such as *Bacillus pseudofirmus* produce peptides that are active at high pH, such as haloduracin that is active against *Enterococcus faecalis* [33].

Such compounds are promising opportunities for developing antibiotics able to stay effective under various conditions in the human body or even in medical devices with pH-varying surfaces.

4.5 Compounds Extracted from Radiophiles

Compounds from extremophiles are increasingly being viewed as a “nature’s arsenal” for the identification of novel antibacterial agents because these organisms have to survive extreme oxidative, desiccation and radiation stresses, which can lead to the evolution of powerful protective chemistries. Mechanistic studies in *Deinococcus radiodurans* have shown that low-molecular-weight metabolites enriched in manganese and phosphate facilitate radiation resistance through a synergistic protection of macromolecules and a reduction in radiation-induced oxidative damage that allows for the preservation of cellular function under harsh insults [34].

Furthermore, studies on manganese ligand systems have increasingly shown how coordination chemistry (e.g., Mn2+ complexation involving phosphate and custom-designed protective peptides) can lead to extremely potent antioxidant activity under ionizing conditions [35]. Although these studies are related to the radioprotection aspect, a more general rationale of discovery can be supported: Metabolites and related peptide/ligand systems from extremophile sources, identified by extraction and activity-guided fractionation, may have antibacterial potential, either by direct antimicrobial activity or by modulating bacterial stress response pathways, especially in pathogens where tolerance to oxidative stress is a major factor in pathogen persistence [34],[35]. Therefore, it is a rational approach to isolate and characterize bioactive fractions from radiophiles and other extremophiles to identify new antibacterial candidates with robustness-enhancing or membrane/protein-targeting properties.

5 Technical Challenges and Future Trends in Exploring Antibacterial Compounds from Extremophiles

Although extremophiles are a great potential source for new antibacterial compounds, there are a variety of technical and methodological challenges to exploit this biodiversity. These challenges are isolation and culture, genetic analysis, and finally the economics and regulations of taking discovered compounds and turning them into clinically useful drugs. Culture-independent pipelines introduce distinct technical challenges at every methodological stage, from initial sampling biases to downstream bioinformatic limitations Figure 1.

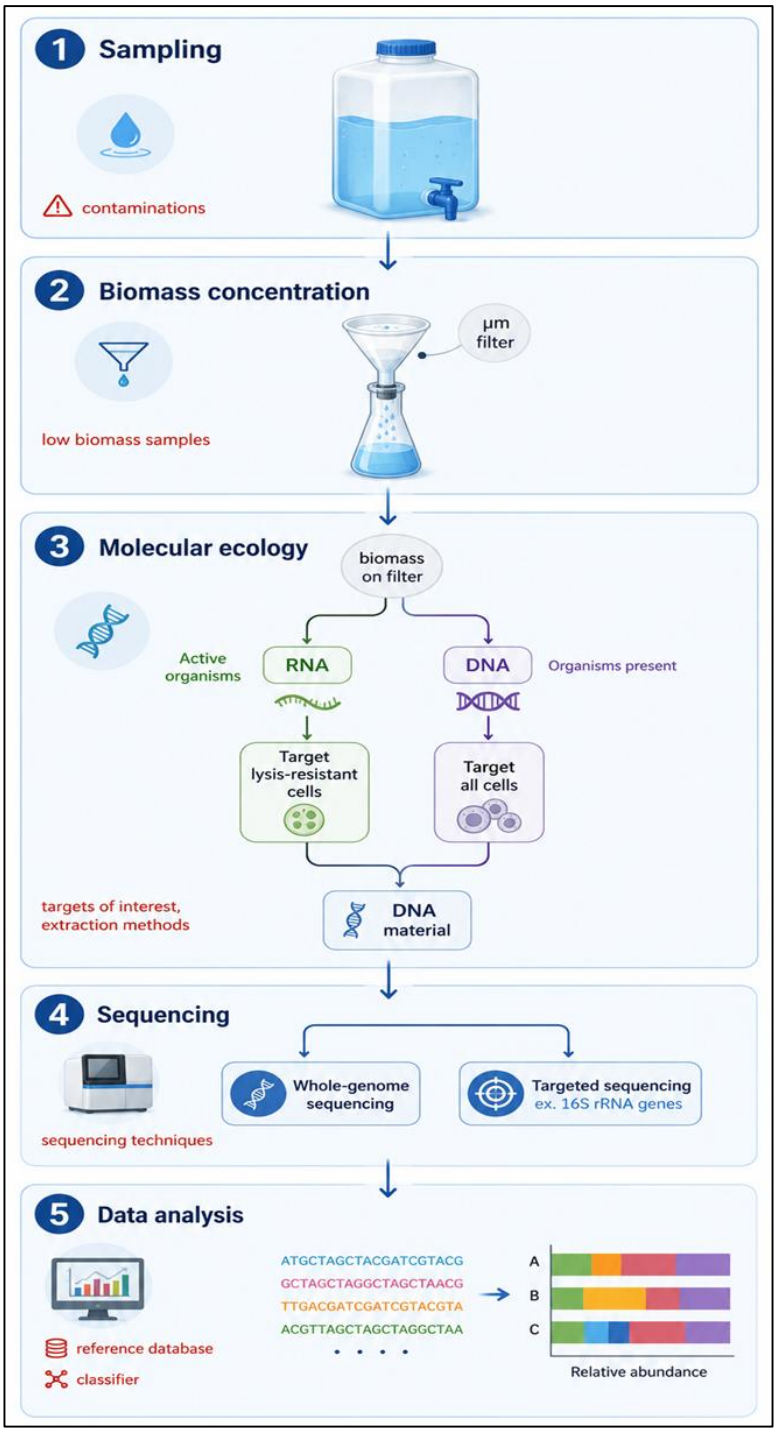


Figure 1: Schematic representation of the culture-independent metagenomic workflow for analyzing microbial diversity. The pipeline details five critical methodological stages sampling, biomass concentration, molecular ecology (DNA extraction), sequencing, and data analysis alongside the primary technical challenges and biases inherent to each step. Adapted from Bregnard *et al.,* (2023) [36].

5.1 Challenges of Isolation and In vitro Culture

Most microorganisms have growth requirements which are difficult to reproduce in the laboratory. More than 99 % of microorganisms cannot be cultured under standard laboratory conditions [37],[38].

Some of these extremophiles cannot be cultured using some microbial culture methods at the nonstandard pressures and salinities that these organisms require. It has been shown that some piezophiles can grow perfectly at pressures of ~40 MPa, while extreme halophiles are generally defined as those that can grow at 10% NaCl or higher [39],[40].

The inability to culture these microbes led to the idea of "microbial dark matter" which accounts for a large portion of microbial diversity that cannot be cultured particularly in extreme environments [37],[41]. To overcome this issue, microfluidic and in situ cultivation systems have been developed to more closely resemble the natural environmental conditions on chip, leading to a higher recovery of the previously uncultured microorganisms compared with traditional cultivation methods [42].

5.2 Genetic Limitations and Genomic Analysis

Many of the genes obtained from genomes and metagenomes of extremophiles are unannotated or have no clear homolog in the reference databases [43]. Furthermore, many genes involved in the production of biosynthetic compounds (biosynthetic gene clusters BGCs) are silent or not expressed under laboratory culture conditions [44],[45],[46].

The silent biosynthetic gene cluster problem has been addressed using metagenomic cloning and heterologous expression in which biosynthetic DNA is inserted into more tractable model hosts, especially *Escherichia coli* and Streptomyces species [47],[48]. This strategy has widened the accessibility of otherwise inaccessible biosynthetic pathways and has been employed to discover or characterize novel natural products such as salinilactam A and abyssomicin-class metabolites [49],[50],[51].

Recently, artificial intelligence techniques have appeared to be a powerful tool for identification of active BGCs. For example, algorithms used in deep learning implemented by the DeepBGC platform could predict the nature of the biomolecules from gene sequences only with an accuracy of more than 80% [52],[53].

5.3 Analytical and Chemical Limitations

There are many reasons why the structural determination of compounds isolated from extremophiles can be difficult. The chemical nature of the metabolites produced by these organisms is often unusual and their isolation and characterization is further complicated by their often very small quantities. Accurate characterization is therefore usually achieved by a combination of high resolution mass spectrometry (including LC-MS/MS) and NMR spectroscopy. These methods provide complementary data, NMR delivering data for detailed structural assignment and mass spectrometry information regarding molecular formula and fragmentation [54],[55],[56].

Things get even more complicated when natural products are derived from very saline environments. Crude extracts can contain high concentrations of salts which interfere with spectrometric analyses and can make characterization by NMR complicated. Therefore, in many cases the crude extracts cannot be directly analyzed and several purification steps are required before the compounds can be confidently characterized. Depending on the nature of the extract and the compound, advanced hyphenated analytical workflows may be required to provide adequate information for unambiguous structure elucidation [57],[58],[54].

Another challenge is that the presence of a biosynthetic gene cluster does not guarantee that its products will be readily detected under laboratory conditions. Many BGCs are silent or produce metabolites in very low amounts. Thus, other strategies such as pathway activation or metabolic engineering or optimization of fermentation conditions might be required to improve the production of metabolites and to obtain enough material for further pharmacological evaluation [59],[60],[61].

5.4 Future Trends in Research and Application

Metagenomic mining, genome-guided biosynthetic analysis and artificial intelligence are increasingly combined to accelerate discovery of new antibacterial compounds as recent studies have shown [62],[63]. This is also aided by synthetic biology that allows the discovery, increases the production and structural diversity of microbial natural products [64].

Very encouraging is the discovery of the extreme environments. These environments, such as hydrothermal vents, hypersaline lakes, deserts and deep sea sediments, continue to produce structurally novel bioactive metabolites [16],[65]. Co-cultivation is a complementary method to mimic ecological interactions to activate silent biosynthetic gene clusters, which generally results in the production of new secondary metabolites with antibacterial and other bioactivities [66],[67]. The combination of these two approaches broadens the chemical space for the discovery of antibiotics and increases the chances of isolating rare compounds with desirable biological properties [68].

On the application side, investing in AI-guided bioprospecting and screening pipelines for antimicrobial discovery have been increased by biotechnology groups; one of the examples is the 2023 discovery of abaucin, a narrow spectrum antibiotic that proven to be active against multi-drug resistant *Acinetobacter baumannii* [69].

6 Conclusion

The recent decades of accumulated scientific evidence suggest that extremophiles are a large biological reservoir of compounds with antibacterial activity especially when considering the worldwide crisis associated with antibiotic resistance.

However, concerted efforts are needed to overcome the technical challenges of isolation, cultivation and extraction to realize their true potential and the urgent need to fund research in this field persists, as many of the habitats where these organisms live are in remote or protected areas.

Recommendations

- Expand the use of metagenomics in genetic exploration of environments.
- Promote cooperation in microbiology, biochemistry and biotechnology.
- Support scientifically supervised sample collection campaigns in extreme environments.
- Construct global gene and compound banks for extremophiles.

The defense of humanity against resistant bacteria may not be found in traditional laboratories but in the depths of the earth and sea where organisms hide which hold the secrets of true defense.

STATEMENTS ON COMPLIANCE WITH ETHICAL STANDARDS

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Disclosure of conflict of interest

The authors declare that they have no competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Author Contributions

K.A.M. and H.A.S conceived the concept, designed the structure, and performed the primary literature review. Z.H.A. contributed to the literature collection, data synthesis, and drafting of the manuscript. All authors critically revised and approved the final manuscript.

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