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Ecological context for bacterial natural products discovery

Jonathan Parra, [ab] Marla I. Macias-Contreras, [c] Dulce G. Guillén Matus [d] and Katherine R. Duncan *[e]

Covering: This review covers literature from 2015 to present.

It is widely recognised that there is a significant gap between bacterial natural product potential and detected/described products. As such, there are several recent reviews on elicitation strategies for natural products discovery, which are often laboratory focused. Recently, a move to more ecology-focused approaches to understand the function of metabolites in nature and what impacts expression has been a growing trend. In this review, we aim to capture work done that goes beyond laboratory conditions and address ecological studies focussed on what impacts bacterial chemistry, covering both abiotic and biotic influences. We aim to touch on the impact of biodiversity loss, changes in ecosystems and future climate parameters and the implications this will have on natural products chemistry and biodiscovery efforts, the scale and consequences of which are not known.

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1. Introduction
2. Understanding the ecological roles of bacterial natural products
3. Abiotic parameters and their simulation in the laboratory
4. Studying bacterial ecological interactions in the laboratory
5. Culturing bacteria in the field
6. Mining environmental DNA for bacterial natural products
7. Bacterial natural products chemistry in the field
8. Future directions in a changing planet
9. Conclusions
10. Author contributions
11. Conflicts of interest
12. Data availability
13. Acknowledgements
14. References

1. Introduction

Microorganisms from diverse lineages produce an extraordinary repertoire of specialised metabolites (also known as secondary metabolites or natural products) that allow them to thrive in the environments they inhabit. Far from being simple metabolic by-products, these compounds fulfil essential ecological functions, ranging from communication to competition, enabling organism adaptation to dynamic environmental conditions.[1,2] As a result, metabolites such as antibiotics, siderophores, pigments, biosurfactants, or signalling compounds should be understood as chemical mediators of interactions that occur in specific contexts, where physical[3] and biological[4] gradients ultimately define both their expression and function. Recognising the ecological role of these metabolites is crucial, since most studies on bacterial natural products are still conducted under laboratory conditions, which limit and simplify our ability to connect biosynthetic potential with gene transcription and metabolite production.[5]

This review aims to place current research on natural products within an ecological context, discussing how environmental factors determine metabolite regulation, how environmental conditions can be simulated in the laboratory, and what opportunities and challenges arise for the discovery of novel chemistry. We would like to highlight there are some excellent reviews on related topics, including organism interactions[6] and exploring the ecological context for metabolite elicitation in soil communities.[7] For this purpose, in this work, the term "environment" (or environmental conditions) will be

[a]Centro de Investigaciones en Productos Naturales (CIPRONA), Universidad de Costa Rica, San José 11501-2060, Costa Rica
[b]Centro Nacional de Innovaciones Biotecnológicas (CENIBiot), CeNAT-CONARE, San José 1174-1200, Costa Rica
[c]Strathclyde Institute of Pharmacy and Biomedical Sciences, University of Strathclyde, Glasgow, G4 0RE, UK
[d]Facultad de Ciencias Marinas, Universidad Autonoma de Baja California, Carretera Ensenada-Tijuana, Km 103, Ensenada Baja California, 22860, Mexico
[e]Newcastle University, Biosciences Institute, Framlington Place, Newcastle Upon Tyne, NE2 4HH, UK. E-mail: Katherine.Duncan@newcastle.ac.uk

used to refer to the set of biotic and abiotic factors that modulate the production of bacterial specialised metabolites and include chemical, physical, and biological variables.

2. Understanding the ecological roles of bacterial natural products

Among the diverse strategies bacteria employ to adapt to their environments, the production of specialised metabolites is particularly significant, as they enable the strain to compete, adapt and communicate in dynamic ecosystems.[1] A fundamental ecological function of these metabolites is defence, where antibiotics and antifungals act as potent agents of interference competition. By eliminating rivals, they provide niche protection and actively shape the composition of the microbial community.[2] Equally important is resource acquisition, especially under limiting conditions. Siderophores exemplify this function: by tightly binding and mobilising metals such as iron, they enable bacterial persistence in metal-scarce environments, conferring a strong selective advantage.[8] Beyond these functions, specialised metabolites are key mediators of communication and collective behaviours. Quorum-sensing signals, such as γ-butyrolactones produced by Actinomycetota or acyl-homoserine lactones produced by Gram-negative bacteria, have been shown to enable microbes to coordinate responses at the population level.[9] Once signalling molecules reach a threshold concentration, they can trigger multicellular processes, such as sporulation, biofilm formation, and activation of specialised metabolism.[10] Biosurfactants further contribute to this social dimension by facilitating mobility, shaping biofilm

Jonathan Parra

Dr Jonathan Parra is a scientist based in Costa Rica with an interest in integrating omics technologies to study natural products from actinomycetes and better understand their ecological role in nature. After completing a Pharmacy degree and an MSc in Chemistry at the University of Costa Rica, he obtained a PhD in Pharmacy and Biomedical Sciences at the University of Strathclyde, Glasgow, working in the field of antibiotic discovery from marine actinomycetes. Currently, he is an associate researcher at the Natural Products Research Centre (CIPRONA) at the University of Costa Rica and at the National Centre for Biotechnology Innovations (CENIBiot).

Dulce G. Guillén Matus

Dr Dulce Guillén Matus is currently a postdoctoral fellow in the Universidad Autonoma de Baja California at the Marine Science Department. She earned her PhD in Marine Biology from UCSD at the Scripps Institution of Oceanography in 2022, under the supervision of Prof. Paul R. Jensen, where she researched the vertical inheritance of biosynthetic gene clusters in newly divergent species from the Actinomycetota genus Salinispora*. Currently her research focuses on using metabolomic and multiomic approaches, for the study of chemical ecology on host-microbiome-environment interactions in marine systems.*

Marla I. Macias-Contreras

Dr Marla I Macias-Contreras is an oceanographer originally from Ensenada, Mexico. She obtained her BSc in Oceanography from the Autonomous University of Baja California, followed by an MSc in Marine Biotechnology from the Ensenada Center for Scientific Research and Higher Education (CICESE), Mexico. She recently completed her PhD at the University of Strathclyde, UK, where her research focused on comparative metabolomics and genomic analysis of actinomycetes. Her work explores the discovery of marine natural products, in particular, bioactive compounds produced by actinomycetes such as Rhodococcus *and* Micromonospora*. She has over 10 years of experience in marine microbiology and biotechnology.*

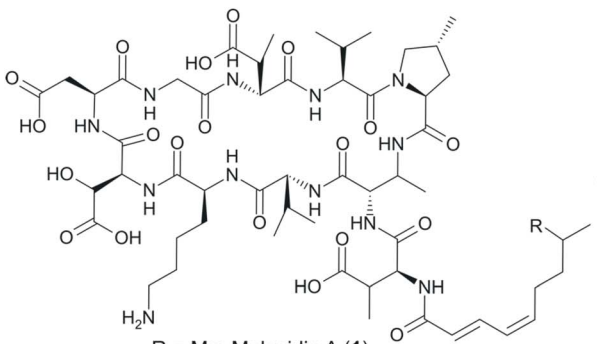
Katherine R. Duncan

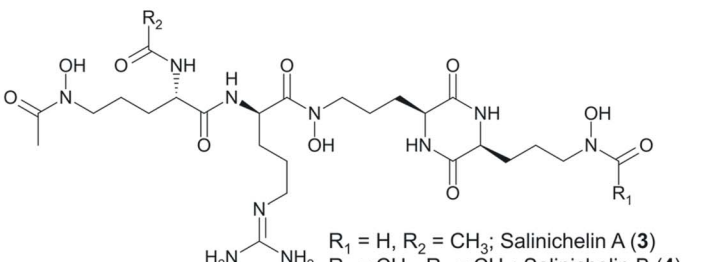
Dr Katherine R. Duncan is an Associate Professor of Microbial Metabolomics and Antibiotic Discovery at Newcastle University, UK. She has an MChem from the University of Aberdeen with international placement at Florida Atlantic University and PhD in Biomedical Sciences from the University of Prince Edward Island, Canada. She completed two Postdoctoral Fellowships at Scripps Institution of Oceanography, UCSD (California) and at The Scottish Marine Institute before starting her lab as a Chancellor's Fellow at the University of Strathclyde, UK (2016-2020). She was awarded tenure in 2020 and in 2024 she moved her group to Newcastle University.

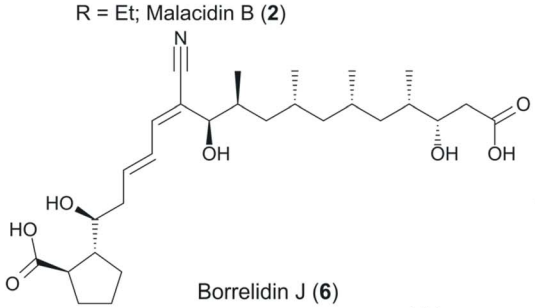
Table 1 Examples of bacterial specialised metabolite ecological functions

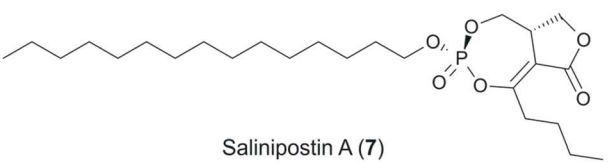
Functional category	Ecological role	Examples
Antibacterials	Defence, niche protection, interference competition	Malacidins **1-2**, calcium-dependent antibiotic from soil[20]
Siderophores	Resource acquisition under iron limitation, survival advantage	Salinichelins **3–5**, siderophores replacing desferrioxamine by *Salinispora*[21]
Antifungals	Defence against fungal competitors, control of microbial community composition	Borrelidin J **6**, antifungal from co-culture of *Streptomyces rochei* and *Rhinocladiella similis*[22]
Quorum sensing signals	Coordination of multicellular behaviours: Biofilm formation, sporulation, specialised metabolism	Salinipostin a **7**, unusual gamma-butyrolactone with a phosphotriester motif[23]
Pigments/protective compounds	Protection from environmental stressors, potential signalling or deterrence	Indigoidine **8**, blue pigment from *Streptomyces* which production is induced by light[24]
Surface-active agents (biosurfactants)	Biofilm structuring, swarming, defence, facilitating access to nutrients	Biosurfactants identified from marine sediment bacteria.[25,26]
Ecological modulators/plant interaction compounds	Root colonisation, mutualism, and modulation of plant immune responses	Anisomycin **9**, *Streptomyces* metabolite that inhibits the infection of tobacco mosaic virus (TMV) and potato virus Y (PVY) by inducing host defense responses[27]

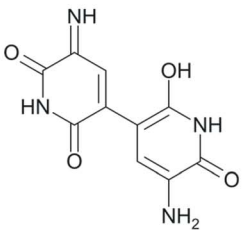
architecture, and improving access to otherwise unavailable nutrients, reinforcing the importance of bacterial chemistry in structuring cooperative and competitive behaviours.[11] Specialised metabolites also support bacterial persistence under abiotic stress. For example, pigments such as melanin and carotenoids have been shown to protect cells against oxidative stress, desiccation, and UV irradiation, functions that are especially advantageous in extreme or fluctuating habitats.[12,13] Finally, specialised metabolites can also work as ecological modulators of host interactions. Metabolites often described solely as antimicrobials may, in ecological contexts or in lower concentrations, operate instead as signalling molecules, for

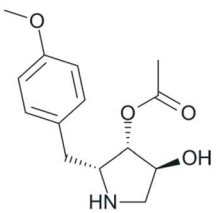








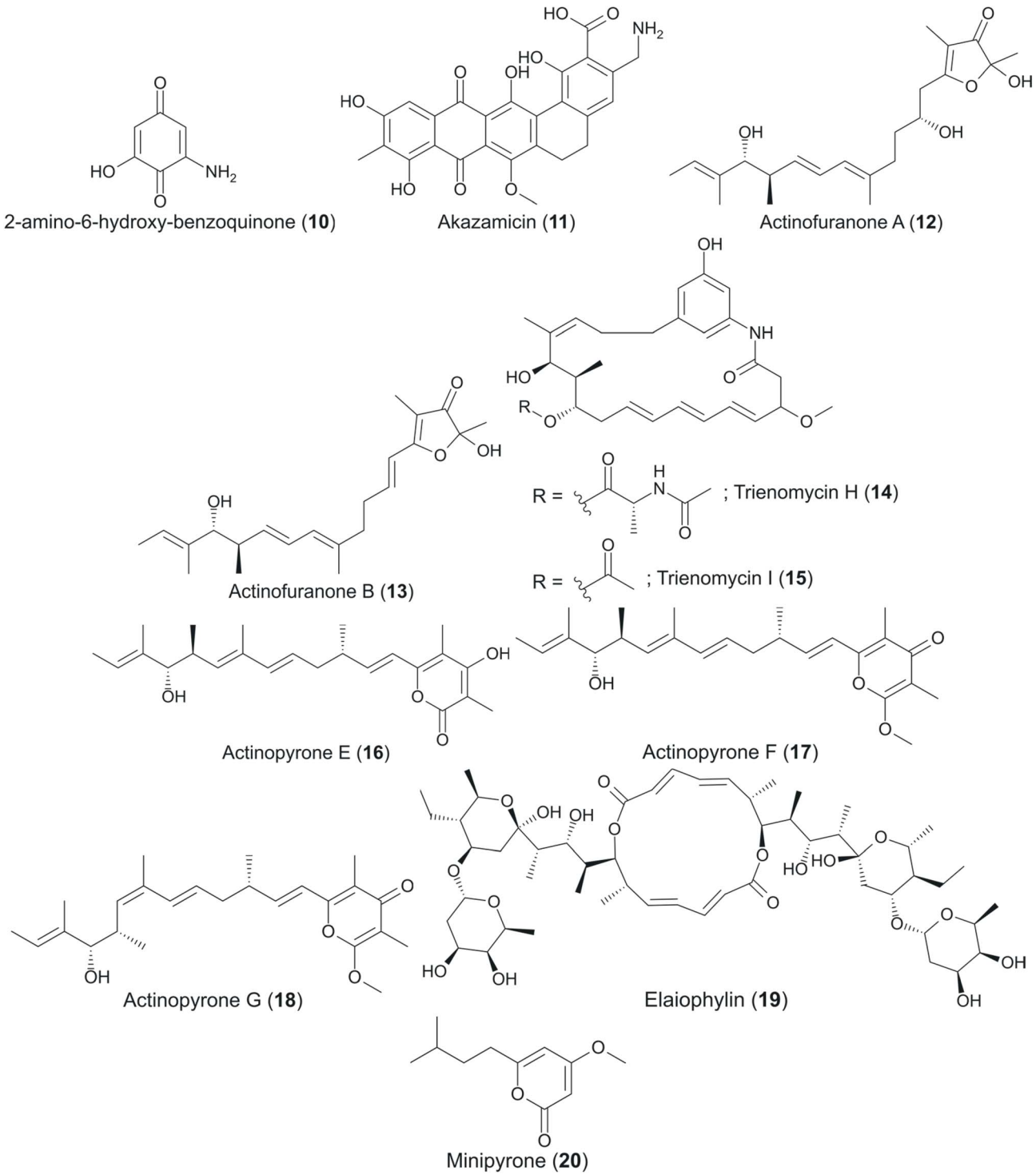




example, during plant colonisation, symbiosis, or host immune responses.[14,15] Horizontal transfer of biosynthetic gene clusters further amplifies these functions by enabling the dissemination of genes across taxa, allowing microbial populations to adapt to new environments or exploit novel ecological opportunities.[16]

These diverse functional categories highlight how bacterial metabolites underpin survival, competition, and communication across ecological contexts. Representative examples are summarised in Table 1. Among these ecological interactions, the producing organisms must develop self-resistance mechanisms to prevent bioactive natural products from having toxic effects on themselves. Thus, the co-localisation of resistance genes and biosynthetic genes results in a strategy for the study of natural products, and is the subject of analysis in other notable reviews.[17,18]

Extreme or rapidly changing habitats, such as those with high salinity, nutrient limitation, intense radiation, or thermal

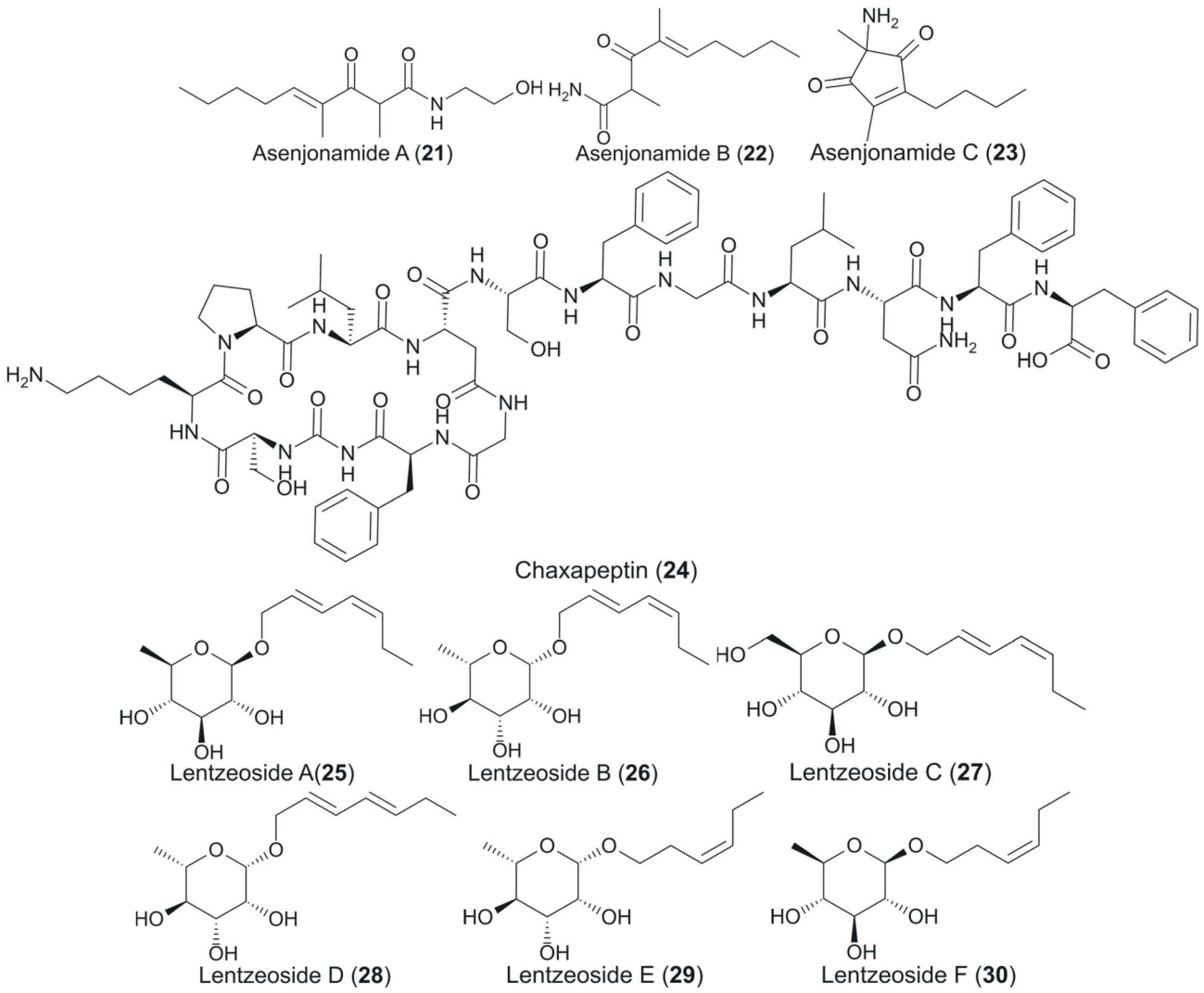


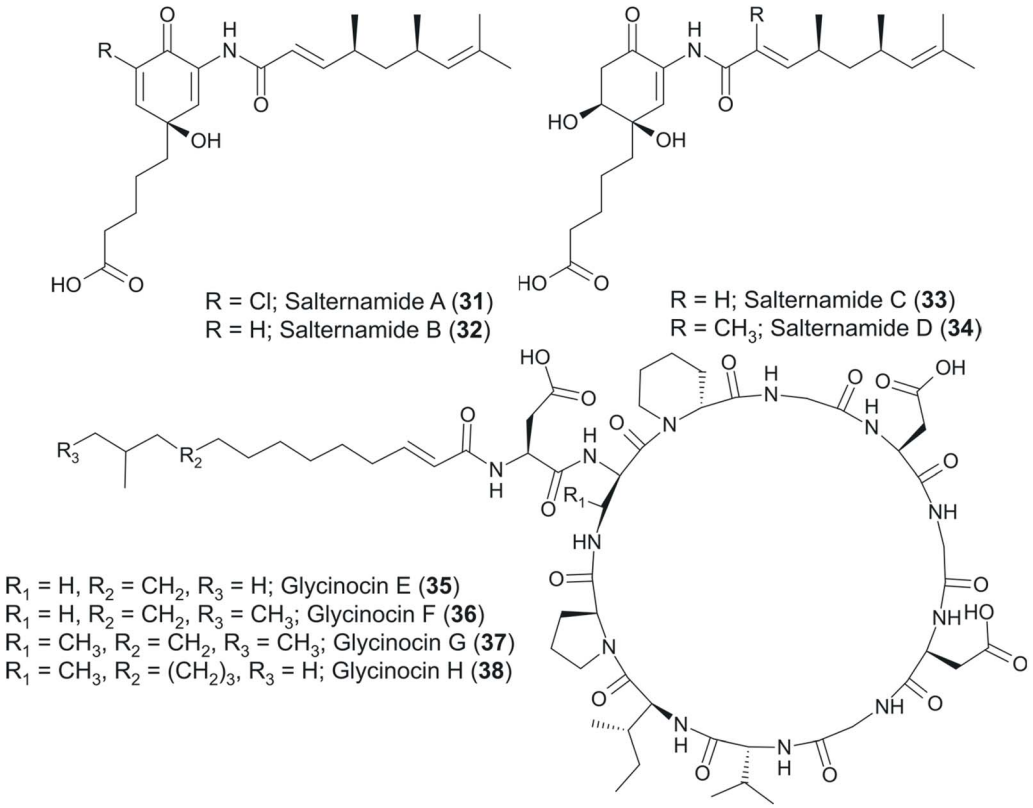
stress, have been shown to promote the activation of distinctive metabolic pathways, leading to the production of compounds rarely observed under standard conditions.[19] These environments therefore not only serve as reservoirs of novel chemistry but also provide natural laboratories for understanding how microorganisms fine-tune their metabolism in response to ecological pressures.

The extremobiosphere includes a wide array of habitats such as hyper arid deserts, deep-sea sediments, hydrothermal vents, permafrost soils, and acidic or high-temperature ecosystems. These environments are defined by combinations of extreme abiotic parameters, including anoxia, aridity, temperature extremes, high salinity, low nutrient availability, and intense radiation. The search for novel bioactive compounds in these settings is based on the premise that harsh conditions select for microorganisms that have adapted to these extremes and therefore, the rationale is that they may produce chemically distinct metabolites.[28] Deep sea bacteria have emerged as particularly promising reservoirs of bacterial and chemical diversity.[29] For example, the anticancer metabolites 2-amino-6-hydroxy-benzoquinone **10**, akazamicin **11**, actinofuranones **12-13**, and trienomycins H and I **14–15** were isolated from a thermophilic-vent *Geobacillus* sp. E263, *Nonomuraea* sp. AKA32 from deep sea sediment, and *Ochrobactrum* sp. OUCMDZ-2164 from abyssal plains of the South China Sea respectively.[30–33] Other examples of antimicrobial metabolites include actinopyrones E–G **16–18**, elaiophylin **19**, and minipyrone **20** produced by *Streptomyces* sp. SCSIO ZS0520 isolated from a hydrothermal vent.[34,35]

Historically, hyper-arid environments have been widely studied in the search of new natural products. Some examples include asenjonamides A–C **21–23**, antibacterial metabolites isolated from *Streptomyces asenjonii*,[36] the lasso peptide chaxapeptin **24** from *Streptomyces leeuwenhoekii*,[37] and lentzeosides A–F **25–30** from *Lentzea* sp.,[38] all isolated from the Atacama Desert.

Additionally, the study of hypersaline habitats like solar saltern led to the discovery of salternamides A–D **31–34** from a halophilic *Streptomyces* strain.[39] Similarly, glycinocins E–H **35–38** were discovered from gypsum-soil-associated *Streptomyces*, an environment characterised by dry and warm conditions.[40] Although the direct ecological functions of many of





these compounds remain experimentally underexplored, the recurring discovery of metabolites with defensive or protective activities (*e.g.*, akazamicin, actinopyrones) from extreme habitats, together with compounds associated with tolerance to harsh conditions such as high temperatures (*e.g.*, glycinocins), suggests a potential adaptive relevance in these environments.

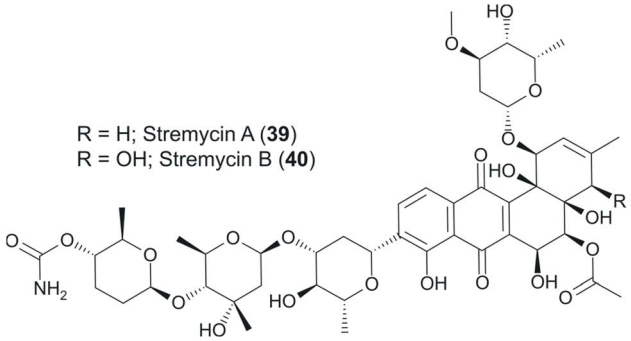
Within this framework, it becomes particularly relevant to explore how microorganisms respond to extreme conditions, whether related to temperature, pressure, salinity, or nutrient availability. Studies on extremophiles, as well as models simulating environments such as outer space, polar deserts, or hypersaline systems, have demonstrated that these stressors not only affect bacterial survival but also drive specialized chemistry.[6,12,57] These examples open new perspectives on how metabolite regulation and expression occur in unconventional environmental contexts.

In summary, studying the biosynthetic potential of microorganisms from an ecological perspective implies recognizing their complexity and dynamism. Microbial environments are not static; they are systems modulated by multiple abiotic and biotic factors, in addition to microbial interactions and their metabolic responses. Based on this, the following section will address how these parameters can be simulated in the laboratory, from the adjustment of individual variables to the use of microcosms or more complex technological systems, to bridge the gap between genetic potential and observable chemical production under culture conditions.

3. Abiotic parameters and their simulation in the laboratory

Abiotic conditions exert a profound influence on bacterial metabolism, with factors such as metal ion concentration, salinity, pH, temperature, and light intensity all reported to modulate the type and quantity of specialised metabolites produced. In addition, nutrient availability, often shaped by both abiotic and biotic processes, also plays a key role in regulating bacterial metabolic outputs. However, not all abiotic manipulations performed in laboratory studies reflect ecologically relevant conditions, and in many cases are instead used as general strategies to activate silent biosynthetic pathways. For instance, variations in carbon and nitrogen sources have been shown to trigger biosurfactant production by *Pseudomonas aeruginosa*,[42] while nitrogen limitation in the permanently anoxic Cariaco Basin reshaped metabolite profiles of free-living microorganisms.[41] Similarly, nickel availability induced the biosynthesis of the antibiotics stremycins A and B **39-40** by the marine *Streptomyces pratensis* strain NA-ZhouS1.[43] Salinity and temperature also shape bacterial metabolism: in *Vibrio* species, they modulate the production of the pigment prodigiosin,[44] while in the psychrotolerant micromycete *Penicillium vulpinum* KPB F-290, changes in cultivation temperature directly influenced the biosynthesis of antimicrobial β-lactams and peptides.[45] Light intensity and wavelength further regulate metabolic output, particularly in photosynthetic microbes,

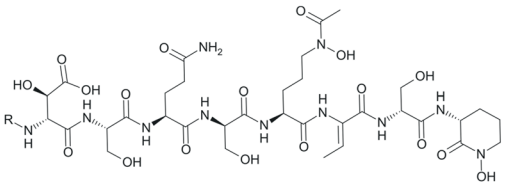
where distinct spectral ranges have been linked to the production of pigments and secondary metabolites.[46,47]

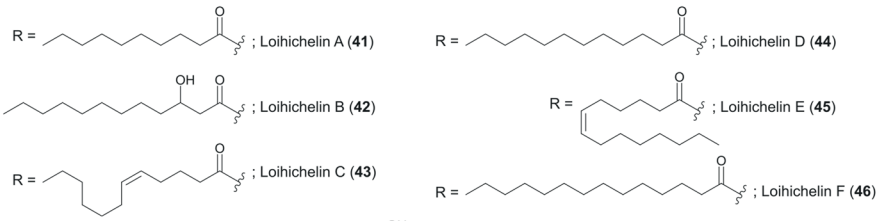


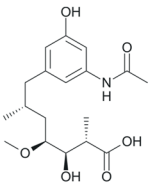
Arguably, the most realistic way to study the impact of abiotic parameters in the laboratory would be through a multifactorial design, yet most work to date has focused on changing single conditions and on chemical elicitors, which are not necessarily natural or in ecologically relevant concentrations.[48,49] For example, monoterpenes (1,8-cineole and linalool) and a sesquiterpene (nerolidol) delivered through an artificial root system have been shown to modulate bacterial and fungal growth.[50] Abiotic environmental conditions, as mentioned before, can include nutrients (*i.e.* culture media), salinity, pressure, temperature, UV and pH and there are excellent reviews on these as strategies for eliciting novel chemistry in the laboratory.[51,52] In this context, metal ion concentrations also provide strong ecological cues: the isolation of loihichelins A–F **41–46**, siderophores from *Halomonas* sp. LOB-5 at the Loihi Seamount reflected a clear adaptation to elevated manganese and iron concentrations, where their metal-chelating properties mirrored the prevailing geochemical conditions.[53] Exciting work on extremophiles, or extreme environments[28] has really demonstrated the impact of these parameters on the microorganisms themselves, including simulating life on Mars (high salinity, low temperature, low pressure) using *E. coli* and *Serratia* to look at bacterial survival and replication[54] and stains from Antarctica as an analogous system for Martian biosignatures characterising iron reduction by *Shewanella*.[55] Yet, while it is common to simulate one parameter to assess phenotype, it is less common to assess the impact on microbial chemistry. For example, light wavelength has been investigated to assess photobiotic response of basidiomycetes, with red wavelengths increasing phenolic compounds and antioxidant bioactivity and blue/white wavelengths increasing fatty acids and carbohydrates. Similar effects have been reported in cyanobacteria, where wavelength-specific responses were linked to the production of pigments and specialised metabolites, directly connecting photosensory pathways with metabolic output.[46,47] The impact of photobiology has also been extensively assessed using microalgae, usually to increase the production of targeted metabolites.[56] Finally, variations of culture pH, although not necessarily intended to mimic environmentally relevant conditions, are often used as a general strategy to promote the production of otherwise silent metabolites. For instance, cultures of *Streptomyces samsunensis* DSM42010 at pH 5.4 showed changes in metabolite profile in comparison to other pH conditions (pH 4.5, 6.6, and 7.4), which led to the discovery of seven new natural products **47–53**, including two geldanamycin analogues.[57] Building on the approach of altering single parameters, local environment has also been simulated, which has included solid keratin/agarose pellets embedded in polyacrylamide gel for skin microbes[58] and a diffusion based integrative cultivation approach (DICA) to isolate novel taxa from marine sediment, labelled a "microbial aquarium" with modified low-nutrient media[59] as well as various diffusion-type set ups to mimic environmental conditions, to culture 'hidden' microbial strains from complex environmental samples.[60] These examples highlight that, while manipulation of abiotic parameters can induce the biosynthesis of novel compounds, such changes are not always driven by conditions reflective of the organism's native environment. This underscores the importance of incorporating ecologically relevant parameters when exploring microbial metabolite production.

4. Studying bacterial ecological interactions in the laboratory

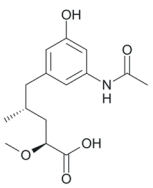
In addition to abiotic factors, microcosms have been a popular strategy to understand both synthetic and natural communities (biotic factors), including spatiotemporal dynamics.[61] For example, the aqueous phases of porous soils and the role of this to shape bacterial soil communities has been investigated using a synthetic community and porous microcosms enabling an understanding of how species level dynamics respond to hydration[62] however, to our knowledge, no new natural products have been isolated from microcosm work, although such approach have been primarily used to investigate the ecological function, regulation, and expression of specialised metabolites and to study BGCs.[4] In addition to microcosms, soil microbe interactions and the impacts of these on natural product production have been reviewed,[63] and in some cases, the function of these biotic interactions has also been categorised into, *e.g.* bacterial cheaters and cooperators and how the benefits of these interactions can be determined by nutrient limitation with a focus on *Pseudomonas* and siderophore production.[64] Yet the complexity of bacterial interactions is challenging to simulate, and as such, most work focuses on co-culture, which has been the subject of recent reviews.[65,66] For example, hydrazidomycin D **54**, a new hydrazide-containing natural product, was obtained through the culture of *Streptomyces* sp. RKBH-B178 with a heat-treated *Mycobacterium smegmatis* strain as an 'inducer'[67] and exposure of *Nocardiopsis* to low inoculum intergenic coculture revealed an average increase of mass spectrometry features by 14% compared to monoculture controls and the detection of uncharacterised pyrrolidinyl polyketides, ciromicins A and B **55-56**.[68] When exploiting potential ecological function strategies in the lab, siderophores have been studied extensively. For example, the siderophore foroxymithine **57** was shown to enable *Streptomyces* colonies to



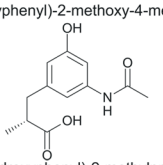




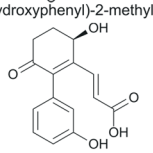
8-(10-Acetamido-12-hydroxyphenyl)-3-hydroxy-4-methoxy-2,6-dimethylheptanoic acid (**47**)



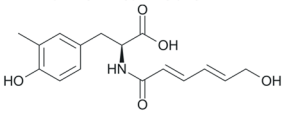
6-(8-Acetamido-10-hydroxyphenyl)-2-methoxy-4-methylpentanoic acid (**48**)



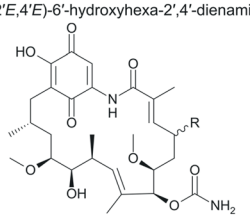
4-(6-Acetamido-8-hydroxyphenyl)-2-methylpropanoic acid (**49**)



2*E*-3-[5-Hydroxy-8-oxo-9-(12-hydroxyphenyl)-cyclohex-3-ene]acrylic acid (**50**)

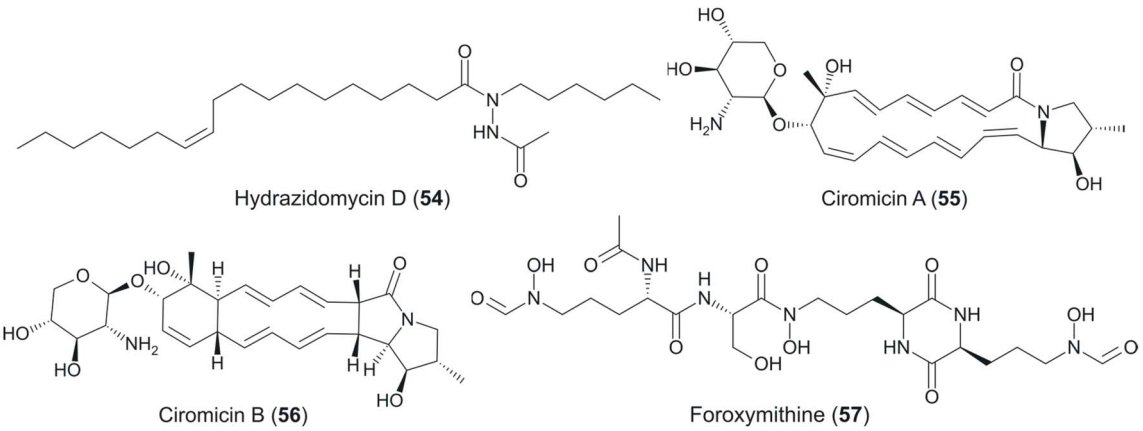


3-(7-Hydroxy-6-methylphenyl)-2-[(2′*E*,4′*E*)-6′-hydroxyhexa-2′,4′-dienamido]propanoic acid (**51**)



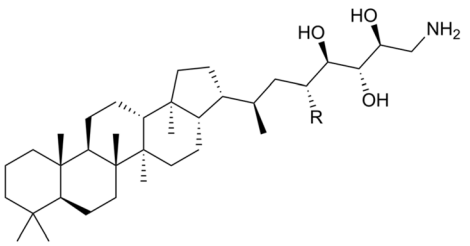
R = ; (4*R*)-4,5-Dihydro-4-hydroxy-17-demethylgeldanamycin (**52**)

R = ; (4*S*)-4,5-Dihydro-4-hydroxy-17-demethylgeldanamycin (**53**)



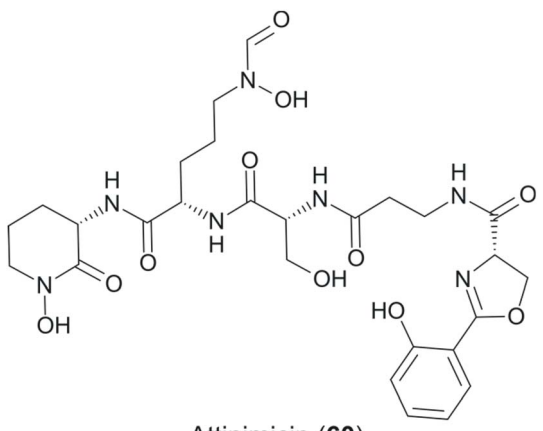
privatise iron around colonies, suggesting that it may play a role in enhancing fitness when in polymicrobial communities.[69]

Innovative methods and technologies have enabled this study of interactions, this includes metaFISH (combining MALDI-MSI with fluorescence *in situ* hybridization (FISH)) to profile the spatial distribution of metabolites based on single-cell imaging of nucleic acid probes.[70] Similarly, by combining FISH microscopy with MALDI-MSI, it was possible to image host-microbe symbioses while mapping the spatial metabolome of a deep-sea mussel and its intracellular symbiotic bacteria at the scale of individual epithelial host cells; showing for example, a strong correlation between the distribution of the bacterial hopanoids 35-aminobacteriohopane-32,33,34-triol **58** and 35-aminobacteriohopane-31,32,33,34-tetrol **59** and a methane oxidizer symbiont.[71]



R = H; 35-Aminobacteriohopane-32,33,34-triol (**58**)
R = OH; 35-Aminobacteriohopane-31,32,33,34-tetrol (**59**)

In other host–bacteria systems, such as the Hawaiian bobtail squid (*Euprymna scolopes*), imaging mass spectrometry has been used to observe metabolite-mediated interactions within the light organ. Coupled with mutant phenotypic analysis and molecular networking, this approach led to the identification of the diketopiperazine cyclo (D-His–L-Pro), produced by *Vibrio fischeri*, which is suggested to modulate luminescence and biofilm formation during the establishment and maintenance of symbiosis.[72] Metabolomics has been one of the most useful tools to observe bacterial interactions, as such, in the gut of the honey bee (*Apis mellifera*), a defined bacterial consortium comprising *Gilliamella*, *Snodgrassella*, *Bifidobacterium*, *Bombilactobacillus*, and *Lactobacillus* has been investigated using gnotobiotic reconstitution, metabolomics, RNA interference, and CUT&Tag epigenomic profiling. These approaches revealed that the short-chain fatty acid butyrate, from bacterial origin, functions as a key signaling metabolite that modulates host histone acetylation and lipid metabolism, leading to the production of prostaglandin E2 (PGE2).[73] In contrast, a more traditional natural products discovery approach—combining large-scale comparative metabolomics, activity-guided fractionation, and biosynthetic gene cluster analysis—led to the identification of attinimicin **60**, a nonribosomal peptide siderophore exhibiting iron-dependent antifungal activity, from *Pseudonocardia* spp. associated with fungus-growing ants (tribe Attini). This compound selectively inhibits the specialized pathogen *Escovopsis*, thereby functioning as a defensive metabolite that protects the fungal cultivar integral to the symbiosis.[74]



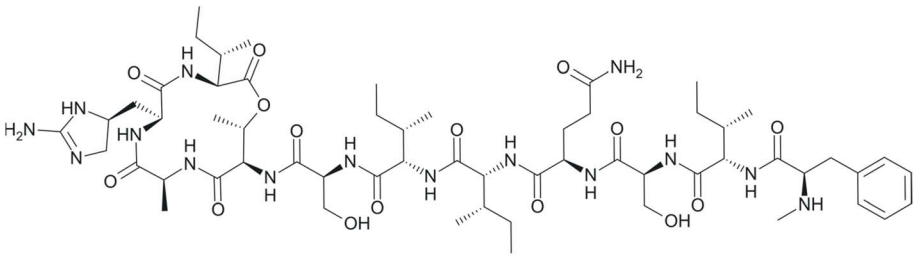
Attinimicin (**60**)

Furthermore, high-resolution secondary ion mass spectrometry (NanoSIMS) and scanning transmission X-ray microscopy (STXM) have been combined to localise single cells with their local environment and profile cellular activities such as carbon/nitrogen turnover with location and chemical speciation information.[75] Methods for enhancing/assessing bacterial growth and metabolites have also been combined

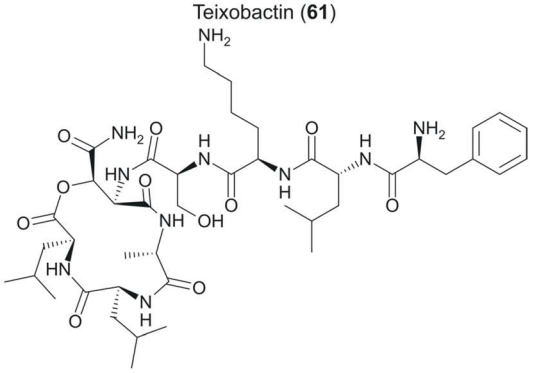
with mathematical modelling studies, such as assessing *Corynebacterium* growth under nutrient-limited conditions (Hornung, 2018).[76]

5. Culturing bacteria in the field

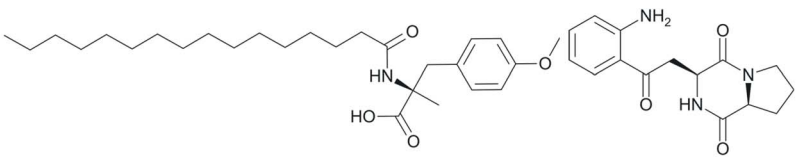
Although recent studies show that the percentage of "culturable" microorganisms (correctly, "cultured") is greater than that predicted by classic culturability paradigms (*e.g.* 1%),[77,78] current laboratory techniques still do not capture the true bacterial diversity that exists in nature.[79] The isolation chip (ichip) is emerging as one of the most promising techniques for isolating microorganisms, previously considered uncultivable, using conventional agar plate-based techniques, although we note that this is still a laboratory-based experiment. The ichip consists of an arrange of miniature diffusion chambers containing a single environmental cell, each with a semipermeable membrane large enough to allow diffusion of important growth factors and nutrients, but not cells.[80] Placing this device back into the environment enables the *in situ* isolation of bacteria that would not grow under laboratory conditions. This approach was used to discover teixobactin **61** from *Eleftheria terrae*, a previously uncultured bacterium.[81] Teixobactin synergistically binds to lipids II and III, essential building blocks of cell wall synthesis, making it the first antibiotic in its class and offering hope for the discovery of a new class of antibiotics.[82] Clovibactin **62**, another nonribosomal peptide also discovered from *Eleftheria terrae*,[83] is another example of this new class of antibiotics.



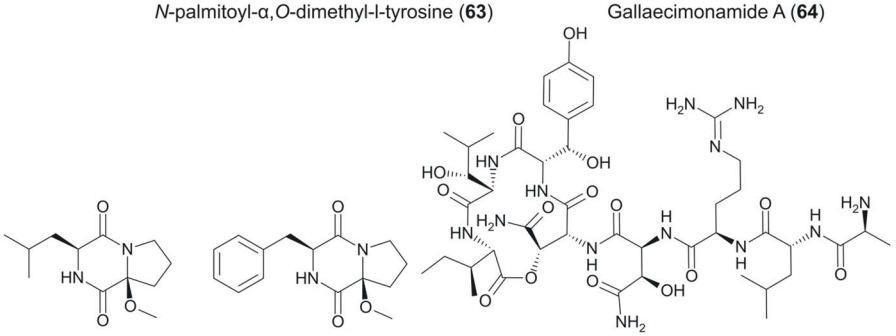
Teixobactin (**61**)



Clovibactin (**62**)



N-palmitoyl-α,*O*-dimethyl-l-tyrosine (**63**) Gallaecimonamide A (**64**)



Gallaecimonamide B (**65**) Gallaecimonamide C (**66**) Hypeptin (**67**)

Further examples of natural products discovered using the ichip device include *N*-palmitoyl-α,*O*-dimethyl-*l*-tyrosine **63** from *Alteromonas* sp. isolated from the tropical marine sponge *Xestospongia muta*,[84] gallaecimonamides A-C **64–66** from *Gallaecimonas mangrovi* isolated from mangrove sediments,[85] and hypeptin **67**, previously isolated from *Pseudomonas*, but described as *Lysobacter*.[86]

6. Mining environmental DNA for bacterial natural products

Historically, most studies on natural products have been conducted under standard laboratory conditions, which has led to a lack of understanding of how these compounds are produced, how they evolve, and what their function is in nature.[63] Arguably, the identification of BGCs in metagenomes and their subsequent heterologous expression represents the clearest route to the culture-independent discovery of natural products (Fig. 1).[87] These studies generally require the mining of a large number of metagenomes to identify BGCs that are novel and viable for heterologous expression. For example, graspetide and spliceotide RiPPs with protease-inhibiting antiviral activity were discovered by heterologous BGC expression following analysis of over 2200 annotated BGCs in over 1300 reconstructed environmental genomes during the study of lake microbial mats.[88] A larger number of environments represents, of course, an analysis scale-up. For example, the metagenomics analysis of more than 1000 seawater samples was conducted to identify over 26 200 reconstructed environmental genomes with the annotation of over 39 000 BGCs, which eventually led to the discovery of two RiPPs by heterologous expression.[89] An alternative to this pipeline is the Metagenomics Identifier of Biosynthetic Gene

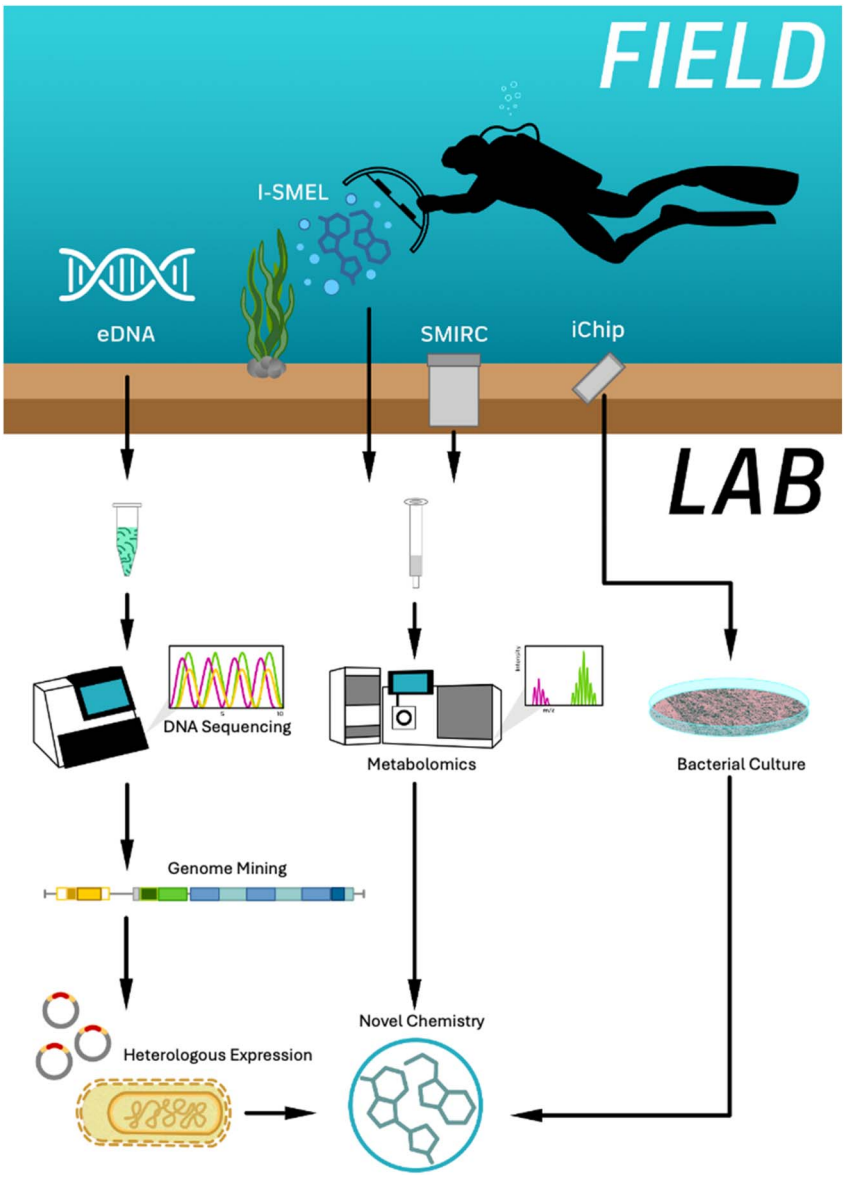
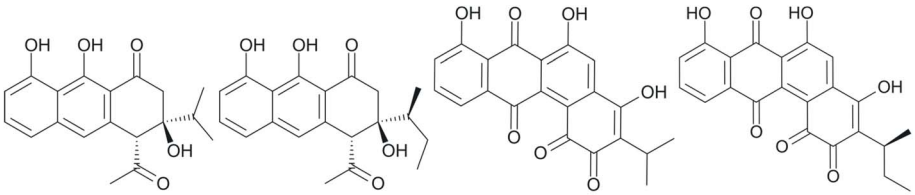


Fig. 1 Strategies for the discovery of natural products directly from the environment.



Clusters (MetaBGC) that allows BGCs detection in sequence data of bacterial communities without prior genome assembly. This strategy was used for the discovery of metamycins A-D **68–71**, new type II PKS products from the human microbiome.[90]

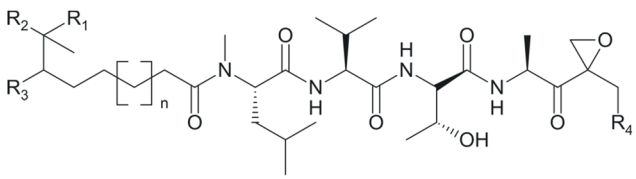
Another example of a tool developed for BGC mining in metagenomes is the environmental Surveyor of Natural Product Diversity (eSNaPD), which uses PCR-generated sequence tags that target conserved biosynthetic domains to facilitate the identification of unexplored natural products chemistry.[91] Using this strategy, the epoxyketone proteasome inhibitors clarepoxcins A–E **72–76** and landepoxcins A and B **77–78** were discovered.[92]

In terms of the origin of the environmental samples, mining the soil metagenome has been the most common strategy for the discovery of natural products from uncultivated microorganisms. For example, the nonribosomal peptides malacidins A and B **1-2**,[20] cadasides A and B **79-80**,[93] omnipeptin **81**,[94] and lapcin **82** (ref. 95) were all described through this approach.

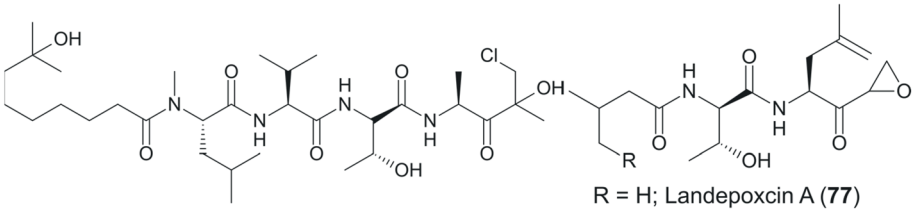
Similarly, hydroxysporine **83** and reductasporine **84** were discovered using a targeted eDNA library construction and mining for rare biosynthetic genes in soil metagenomes[96] and the indolotryptoline motif in lazarimides A–C **85–87**.[97] This type of scaffold for alkaloids was previously illustrated in the structures of BE-54017,[98] and borregomycins,[99] also discovered by heterologous expression of biosynthetic genes annotated in eDNA. Other examples of natural products discovered through soil metagenome mining include the polyene metatricycloene **88**,[100] and the aureolic acids mithramycin **89** and premethramycin **90**.[101]

In addition to soil studies, the metagenome of marine invertebrates has emerged in recent years as a source for the discovery of natural products. The metagenomic study of sponge microbiome-associated cyanobacterial endosymbionts allowed the biosynthetic origin description of naturally produced polybrominated diphenyl ethers (PBDEs) such as 2,4-dibromo-6-(2,4-dibromophenoxy)phenol **91**.[102] Similarly, kasumigamide **92**, previously isolated from the freshwater cyanobacterium *Microcystis aeruginosa*, were described from the metagenome of the marine sponge *Discodermia calyx*.[103]

It is important to note that while biosynthetic gene mining in environmental samples facilitates the discovery of new metabolites, it does not in itself generate information regarding the ecological function of these metabolites in the field. However, combining metagenomic data with other 'omics technologies does allow for an approach to elucidating whether biosynthetic genes are metabolically active in the natural environment. For example, during a metagenomic analysis of microbial diversity and biosynthetic potential in mangrove wetlands, Zhang *et al.*

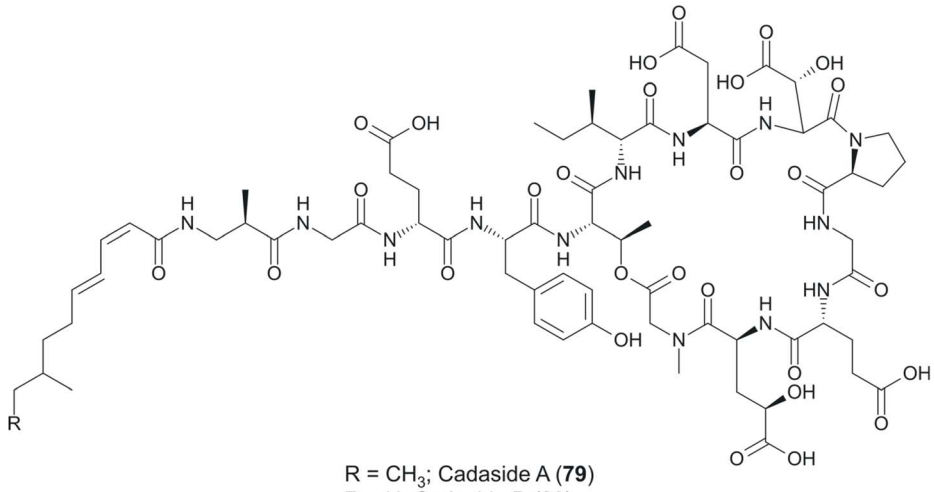


R_1 = OH, R_2 = CH_3, R_3 = H, R_4 = H, n = 2; Clarepoxcin A (**72**)
R_1 = H, R_2 = OH, R_3 = CH_3, R_4 = H, n = 3; Clarepoxcin B (**73**)
R_1 = H, R_2 = CH_3, R_3 = H, R_4 = OH, n = 1; Clarepoxcin C (**74**)
R_1 = H, R_2 = CH_3, R_3 = H, R_4 = H, n = 1; Clarepoxcin D (**75**)

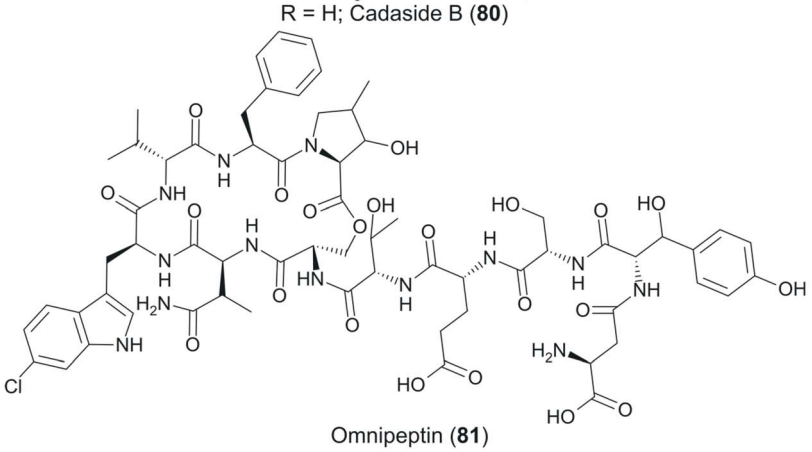


Clarepoxcin E (**76**)

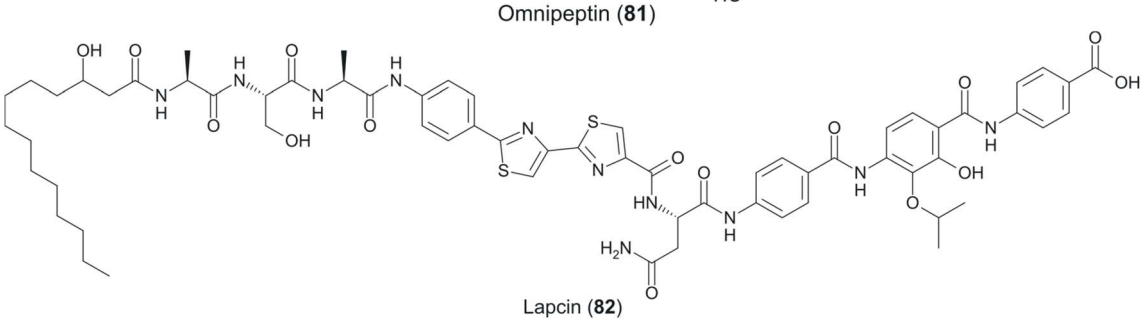
R = H; Landepoxcin A (**77**)
R = CH_3; Landepoxcin B (**78**)



R = CH_3; Cadaside A (**79**)
R = H; Cadaside B (**80**)



Omnipeptin (**81**)

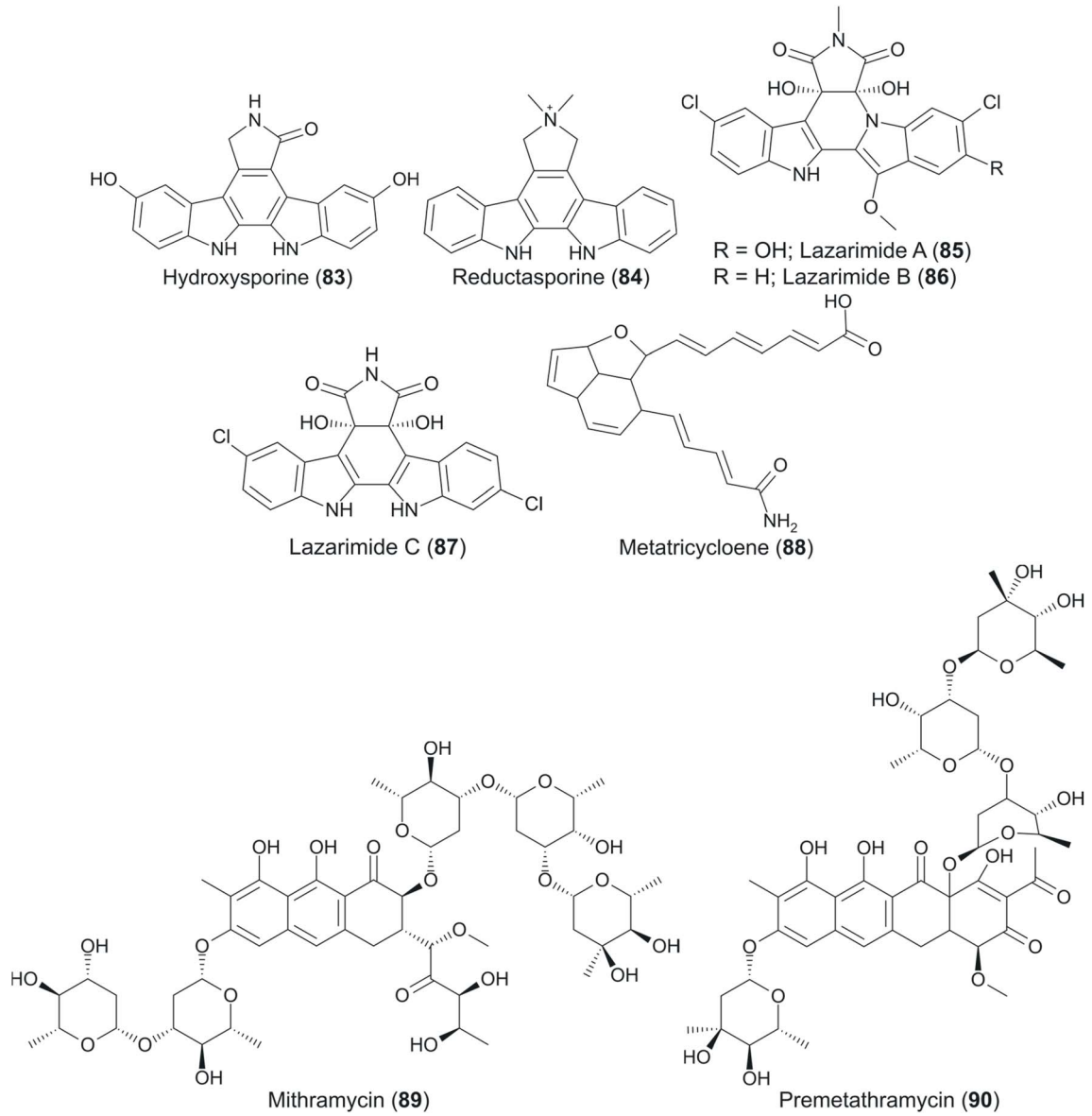


Lapcin (**82**)

(2023) conducted metatranscriptomic analyses of environmental and microcosm sediment samples. The metatranscriptomic reads were mapped to full MAGs to probe the expression of each BGC, detecting the expression of 2689 gene clusters out of 3740 BGCs. This reveals that most of the BGCs identified in the metagenome assembled genomes were active in both the field and microcosm samples (https://doi.org/10.1128/aem.00102-23).[104] A similar metatranscriptomic study in cold seep sediments showed that >73% of bacterial BGCs had active expression at different sites and depths.[105] Another strategy is the direct detection of metabolites in environmental samples and their linkage to biosynthetic genes annotated in metagenomes, which will be explored in the next section.

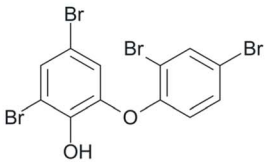
7. Bacterial natural products chemistry in the field

Advances in analytical techniques in combination with novel data analysis approaches have paved the way for metabolomics to study compounds and pathways that mediate ecological interactions.[106] Metabolomics approaches in chemical ecology have been the focus of previous notable reviews.[107,108] In environmental chemistry, the analysis of organic compounds present in soil organic matter and dissolved organic matter in aquatic environments using high-resolution mass spectrometry is a well-established method for the study of biogeochemical cycles such as carbon.[109,110] However, this type of sample comprises a complex molecular mixture, making the full

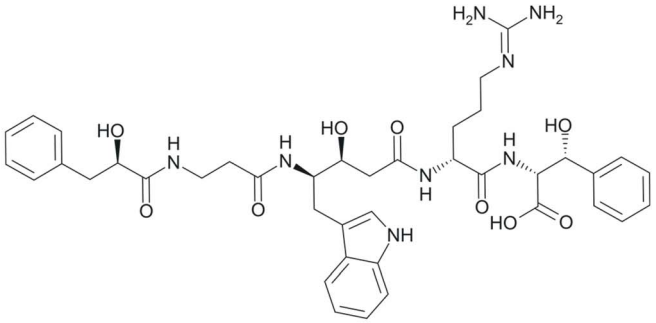


structural characterisation of its components unthinkable to date.[111] Under this scenario, the specific analysis of specialised metabolites becomes a challenging task. However, the application of molecular networking to the analysis of organic matter in environmental samples increases the available molecular information, making it easier to generate more complex analyses of ecosystem chemistry.[112,113] Likewise, the study of metabolite diversity[114] and its integration with metagenomes[115] is proposed as a tool to better understand the structure of metabolomes within the environment (Fig. 1).

In terms of natural product chemistry, the identification and characterisation of specialised metabolites directly from environmental samples represents a culture-independent strategy that could give important insights into the function of these metabolites within ecosystems (Fig. 1). For example, the *in situ* detection of attinimicin **60** from both ant nests and on worker ants supports its proposed ecological role.[74] Moreover, connecting the biosynthetic potential of metagenomes with environmental metabolomes could provide insights into the complex metabolic dynamics of ecosystems. For example, an untargeted metabolomics analysis of marine sediment extracts

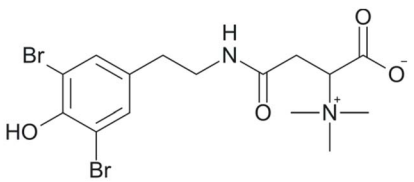


2,4-dibromo-6-(2,4-dibromophenoxy)phenol (**91**)



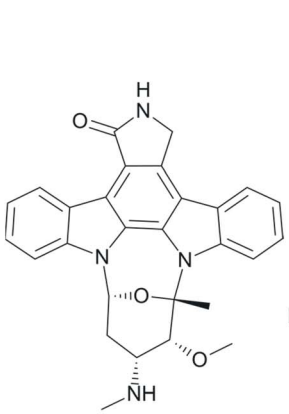
Kasumigamide (**92**)

collected at different locations demonstrated large contrasts in metabolomes between sites, suggesting that metabolites, although generally unknown, likely mediate biological interactions (competition, signalling, defence) and help structure microbial diversity at the local scale.[116] At the same time, the integration of this metabolomics data with genome mining in metagenomes demonstrated that although many detected BGCs did not result in detectable metabolites, correlation between biosynthetic potential and metabolome was observed. For example, the identification of a dibrominated metabolite **93** derived from tyrosine was associated with a *Myxococcota* metagenome assembled genome with the biosynthetic machinery capable of producing it.[116]

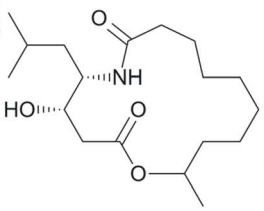


Dibromotyrosine aspartate derived betaine (**93**)

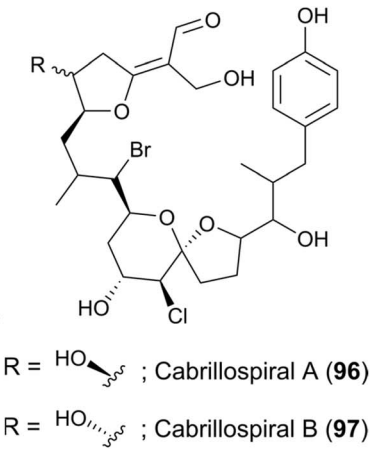
One of the most challenging aspects to face in the direct detection of natural products in environmental samples is the low metabolite concentrations in natural environments. In biotoxin monitoring, absorbent resins have been used for their concentration and subsequent analysis, as in the case of Solid Phase Adsorption Toxin Tracking (SPATT) technology.[117] Following this approach, several solid-phase extraction-based strategies have been developed not only for the detection, but also for the isolation and discovery of natural products. For example, cloth bags containing Diaion™ HP20 adsorbent resin were buried just below the surface of the sediment to be retrieved and extracted 24 h later for HRMS analysis. Several bacterial metabolites were detected, including staurosporine **94**, whose concentration was correlated with the abundance of its putative producer *Salinispora*, *via* metagenomics, suggesting an influence on sediment community structure.[118] This strategy was later named SMIRC (Small Molecule *In Situ* Resin Capture) and used for the discovery of the three new natural products cabrillostatin **95** and cabrillospirals A and B **96-97** from marine environmental samples.[119] The application of this strategy also showed that some environments might have more interesting chemical profiles to explore than others. For example, studying sediments in cold, eutrophic waters may have favoured the



Staurosporine (**94**)

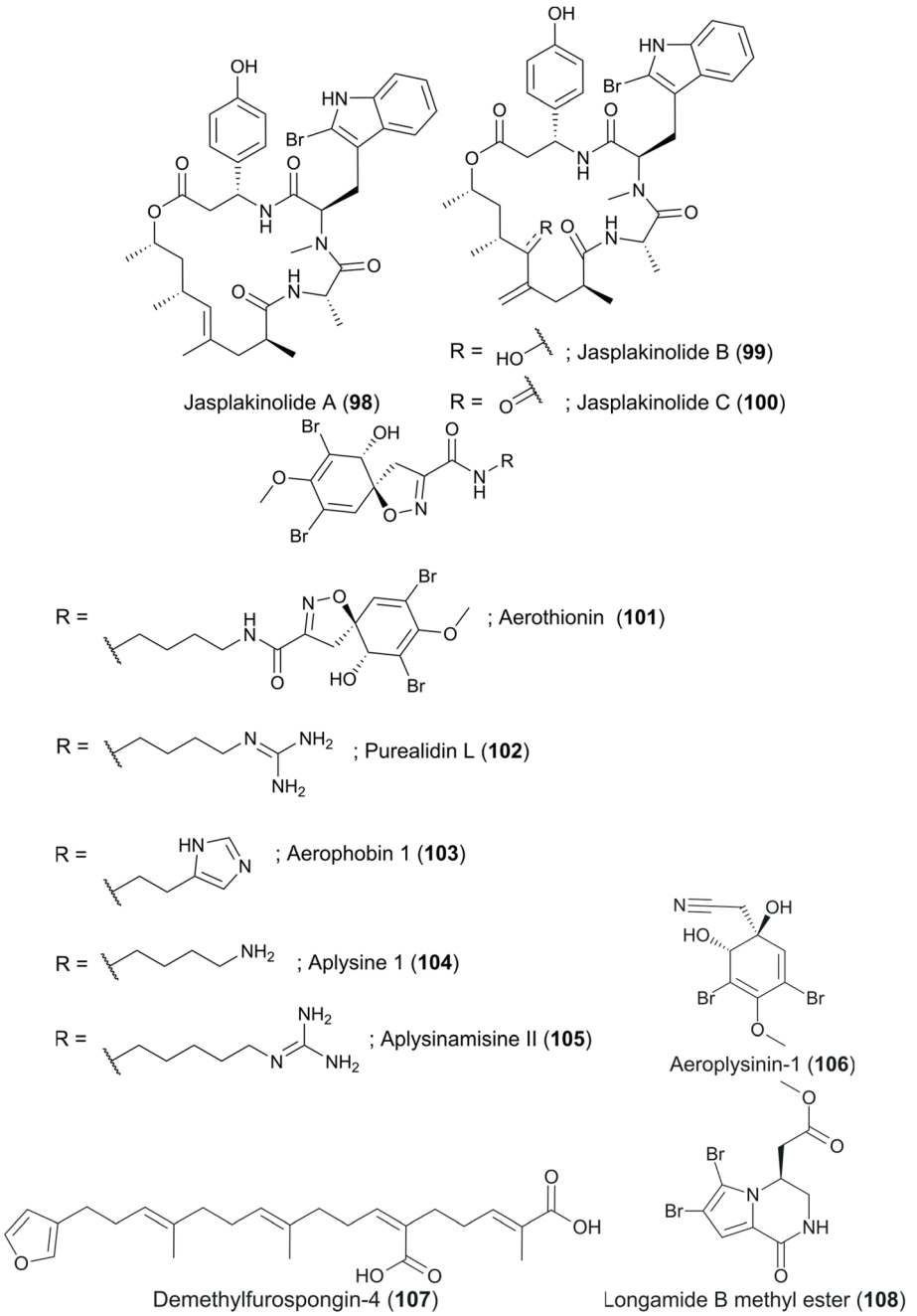


Cabrillostatin (**95**)



R = ; Cabrillospiral A (**96**)

R = ; Cabrillospiral B (**97**)



discovery of new natural products,[109] in contrast to the warm, oligotrophic waters of the first SMIRC study.[108]

An interesting proposal was to create a filtering device that simulated a marine sponge that trapped metabolites in AmberLite™ XAD-18 resin. This allowed the isolation of jasplakinolides A–C **98–100**, previously reported from sponge *Jaspis splendens*, directly in marine environments.[120] I-SMEL (*In Situ* Marine moleculE Logger) is a similar device that was developed to be portable and operated by scuba divers, which contains a divinylbenzene polymer extraction disk that captures metabolites from pumped seawater. By combining this apparatus with HRMS, the identification of marine sponge metabolites, such as aerothionin **101**, purealidin L **102**, aerophobin 1 **103**, aplysine 1 **104**, aplysinamisine II **105**, and aeroplysinin-1 **106** from *Aplysina*, demethylfurospongin-4 **107** from *Spongia*, and longamide B methyl ester **108** from *Agelas*, in environmental samples was possible.[121]

8. Future directions in a changing planet

Climate change is altering microbiomes across diverse ecosystems, with a direct influence on metabolite production and their ecological functioning. In permafrost soils, thawing reshapes microbial communities and metabolomes, favouring stochastic assemblies enriched in carbon-, sulphur-, and nitrogen-containing compounds, which accelerate carbon dioxide and methane emissions.[122] Similar processes occur in other soils, where warming and altered precipitation regimes reduce microbial diversity but stimulate metabolic pathways associated with carbon and nitrogen cycling.[123,124] Climate change has also been associated with an increase in the incidence of wildfires, which has been correlated in metagenomic studies with changes in the soil microbiome, characterised by an increase in the detection of Actinomyccetota encoding genes for heat resistance.[125] Plant-associated microbiomes are likewise sensitive to climate-driven stressors, such as drought and elevated temperatures. For example, a study of the oak seedling microbiome showed a stronger effect of temperature and drought on fungal diversity, as well as a rhizosphere Actinomycetota enrichment, a bacterial group known to increase plant drought tolerance.[126] The ocean, as the largest ecosystem on the planet, is no stranger to these changes. For example, a study of 953 ocean metagenomes collected between 2011 and 2020 found that climate change is expected to alter the ecological status of the surface ocean by influencing environmental conditions, particularly nutrient, carbonate and oxygen content. Microbial population changes such as increased abundance of Cyanobacteria in low-latitude regions, decreases in metabolic pathways related to nitrogen and sulphur cycling in low latitudes, and poleward latitudinal shifts of some dominant microbial groups, such as Proteobacteria, Ascomycota, Bacteroidetes, and Firmicutes, could have an impact on the ecological dynamics of the ocean.[127] Equally significant changes associated with climate change are expected in the deep ocean.[128] In general, the scientific community advocates that changes in the planet's microbiome as a result of climate change will have a profound impact on the environment and irremediably on human health and well-being.[129–131] In this context, the discovery of natural products will be affected by factors such as the loss of biodiversity,[132] habitat loss,[133] and alterations in biosynthetic pathways as a result of biogeochemical cycles changes.[134]

9. Conclusions

The production of specialised metabolites by microorganisms represents a central ecological strategy that underpins survival, competition, and communication across diverse environments. These metabolites work as mediators of complex interactions, and their production is deeply affected by environmental conditions. In this context, integrating ecological perspectives into natural product research represents a powerful strategy to bridge the gap between the vast, yet largely untapped, biosynthetic potential of microorganisms and the comparatively limited set of metabolites detectable using conventional laboratory techniques. By linking natural product discovery with chemical ecology, such approaches provide critical insight into the so-called 'dark matter' of bacterial specialised metabolism, while simultaneously creating new opportunities for the discovery of ecologically relevant natural products. Although this approach is just beginning to bear fruit, it faces the threat of climate change and biodiversity loss, which are restructuring microbiomes, altering metabolomes, and disrupting key biogeochemical processes. Understanding bacterial specialised metabolites within their natural ecological frameworks is, therefore, not only fundamental to advancing our knowledge of bacterial ecology and chemistry, but also a potential tool for anticipating and understanding the impact of climate change on microbiomes in a rapidly changing planet.

10. Author contributions

JP, MC, KRD contributed to the conceptualization and data curation, JP, MC, DG and KRD contributed to the investigation, writing- original draft and writing – review and editing.

11. Conflicts of interest

The authors declare no conflicts of interest.

12. Data availability

No primary research results, software or code have been included and no new data were generated or analysed as part of this review.

13. Acknowledgements

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