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Advances in the discovery and functional analysis of Anti-infective and immunomodulatory natural products from host-associated microbiomes

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Covering: 2018 to 2025

Over recent years, metagenomic-driven studies have revealed an enormous encoded repertoire for the biosynthesis of secondary metabolite scaffolds within host-associated microbiota, yet only a small fraction of these chemical scaffolds has been characterized. This review focuses on recent discoveries of natural products with anti-infective and immunomodulatory properties derived from diverse host-associated microbiomes, covering the period from 2018 to 2025. The selected examples span a wide range of anti-infective and immunomodulatory activities, underscoring the deep integration of microbial secondary metabolism with host physiology, while also highlighting the need for more targeted and efficient combined approaches to fully exploit the predicted biosynthetic capacity of microbiomes for anti-infective research and beyond.

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1 Introduction

Across the vast spectrum of biological life forms, close associations with microbial partners are the rule rather than the exception. Higher eukaryotes typically harbour microbial consortia on their external surfaces and within their gastrointestinal tracts, often consisting of hundreds of species that can alter over the course of development and in response to environmental perturbations.[1–4] Within these consortia (herein referred to as the 'microbiome'), microorganisms interact in complex multispecies networks rather than isolated entities, and their collective activities influence host fitness through nutrient acquisition, but also immune modulation, and defence against pathogens.[5,6] A key component of these contributions is the biosynthesis of bioactive compounds, which has been shaped by co-evolutionary processes and refined through host-

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microbe interactions. The structure-specific bioactivities of natural products help to maintain the balance between the host, its beneficial symbionts, and potential invaders by contributing to defence, immune modulation, and intercellular communication.[7,8]

In particular, advances in short and long-read sequencing technologies and bioinformatics-driven tool development (*e.g.* antiSMASH,[9] Rapid ORF Description & Evaluation Online (RODEO)[10]) and curated databases (MIBIG,[11] MITE,[12] Antishmash database[13]) have enabled the mapping of extensive biosynthetic diversity encoded for natural products in the form of largely uncharacterized biosynthetic gene clusters (BGCs), underscoring the remarkable chemical diversity harboured by microbial consortia.[3,14–16]

In recent years, much emphasis has been placed on the analysis of the human gut microbiome;[17,18] however, diverse terrestrial hosts, including insects,[19,20] avian[21] species, and other animals,[22] as well as pseudoorganisms such as amoebae, have emerged as equally vast and largely untapped reservoirs of BGCs and thus, natural product diversity (Fig. 1). These systems have therefore been proposed to serve as sources of urgently needed leads for antimicrobial,[23] cytotoxic,[24] and immunomodulatory[25,26] agents. However, isolation of natural products from most members of dedicated microbiomes remains intrinsically challenging due to the inability to readily isolate or cultivate a substantial proportion of human-associated microorganisms, and by low availability of the produced natural products under most laboratory conditions.[27–29] Many taxa depend on highly specific environmental conditions, such as strict anaerobiosis, host-derived nutrients or interspecies chemical cues,[30] that are difficult to reproduce *in vitro*. Consequently, the biosynthetic potential of these uncultivated microorganisms remains largely inaccessible to classical cultivation approaches, but more frequently become accessible due to advances in heterologous expression approaches.[31,32]

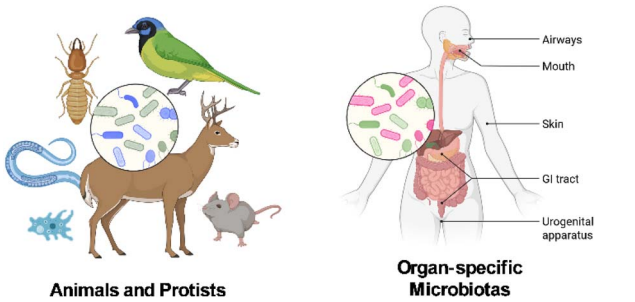

Fig. 1 Examples of organisms and organs that host habitat-specific microbiotas, which act as reservoirs of novel natural products with anti-infective properties.

In this review, we summarize our current knowledge (2018–2025) on primarily isolated and experimentally validated natural products with anti-infective and related immunomodulatory effects that are derived from members of different host-associated microbiomes. Following common usage in the field, we define the collective microbial community and its genomic content within a specific host environment as the microbiome.[33] Consequently, we excluded natural products originating strictly from endosymbiotic interactions in fungi,[34] plants, and insects, as these are highly specialized two-organism systems.[35,36] Examples derived from freshwater and marine microbiomes, though highly relevant,[37–41] fall outside

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the scope of this review and are discussed elsewhere.[42] Similarly, soil[43] and plant[44] microbiome-derived anti-infective natural products are referenced only where their chemistry intersects with the ecology of soil-dwelling insects and animals.

The review is organized by host systems, beginning with examples from pseudo-organisms, followed by the extensive work on invertebrate microbiomes, and culminating in studies of vertebrate microbiomes. Selected examples in each chapter are discussed in the host-specific context they have been discovered, and structured along the approaches that have been employed. Approaches include ecology- and genome-based discoveries using wild-type production as well as molecular biotechnological approaches.[33]

Selected natural product examples either possess a defined ecological role with potential relevance to health or disease or exhibit measurable biological activity against pathogens. In the latter case, key activities are reported as activity ranges or minimal inhibitory concentration (MIC) values, as described in the referenced original literature. Consequently, studies reporting only predicted molecules without experimental confirmation are not discussed in detail.

2 Protists and their bacterial assemblages

2.1 Amoeba (pseudoorganism hosts)

Amoebae are commonly defined as a unicellular organism capable of changing its shape by extending and retracting pseudopods. Typically, amoebae ingest food by phagocytosis, extending pseudopods to encircle and engulf live prey or particles of scavenged biomaterial. Among the most well-known amoeboid protists are *Chaos carolinense* and *Amoeba proteus* and the multicellular "social amoeba" or slime mold *Dictyostelium discoideum*. Other notable species include *Naegleria fowleri*, often referred to as the "brain-eating amoeba," and the intestinal parasite *Entamoeba histolytica*, which causes amoebic dysentery.[45] Comparative studies have shown that different amoeba species harbour distinct and stable microbiomes, even when collected from the same environment.[46]

Free-living amoebae such as *D. discoideum*,[47] once viewed mainly as solitary phagotrophic protists, are now recognized as carriers and "farmers" of diverse bacterial communities that effectively constitute their own microbiomes. Studies of *Dictyostelium* and other social amoebae show that their microbiomes differ markedly from surrounding soil in both, diversity and composition, indicating selective association with specific taxa, likely driven by long-term coevolution and niche-specific interactions.[46] However, members of amoeba-associated microbiomes often face intense predatory and competitive pressures, probably favouring the retention or selective activation of BGCs that encode defence-related or quorum-sensing molecules.[48,49] While the selective forces inherent to this predator-prey-symbiont interplay appear to enrich for bacteria encoding chemically diverse and biologically active metabolites,[50] metagenomic and culture-based studies revealed an abundance of silent or conditionally expressed BGCs, many of which likely respond to specific signalling molecules or environmental stimuli found only within the amoebal niche.[51]

In particular, *Pseudomonas*[52] and *Burkholderia*,[53] both encoding exceptional capacities to biosynthesize a diverse set of natural products, are frequent and dominant members of amoeba-associated microbiomes.[54] For instance, *Burkholderia* symbionts have been identified across diverse *Dictyostelium* species and geographic regions, where they confer benefits such as defence against predators or aid in "farming" behaviour, which allows amoebae to carry and seed bacterial food sources across environments (Fig. 2A).[55,56] Several recent studies have shown that *Pseudomonas* strains isolated from fruiting bodies of *Dictyostelium* spp. produce nonribosomal peptides (NRPs) and polyketides (mupirocin) with antibacterial, and amoebicidal as well as antifungal activity (Fig. 2). Genome mining of the amoebal microbiome strain *Pseudomonas* sp. QS1027 [57] revealed the production of the NRPs jessenipeptin and keanumycins A-C (Fig. 2C). While jessenipeptin exhibits strong activity against methicillin-resistant *Staphylococcus aureus* (MRSA),[58] keanumycin A shows only weak activity against Gram-positive bacteria such as *Bacillus subtilis*, *Enterococcus faecalis*, and *Mycobacterium vaccae*, but displays potent amoebicidal and antifungal properties, even against clinically relevant *Candida auris* and *Aspergillus fumigatus* isolates.[59] Complementary studies on plant-associated and soil bacteria, particularly *Pseudomonas* spp., have shown that these organisms defend against eukaryotic predators by producing bioactive natural products, often in cooperation with co-occurring species to enhance protection against predatory amoebae. By producing and secreting, *e.g.*, syringafactins,[60] lipopeptide surfactants, *Pseudomonas* induces the production of peptidases in a co-occurring *Paenibacillus* strain (Fig. 3A). Remarkably, these peptidases degrade the otherwise harmless syringafactins into smaller compounds that exhibit potent amoebicidal activity, thereby protecting both bacterial partners from predation.[61] This modified lipopeptide could be a starting point to develop amoebicidal lead structure against human pathogenic *Acanthamoeba* such as *Acanthamoeba castellanii or Acanthamoeba comandoni*, which can cause *Acanthamoeba* keratitis.

In a related study exploring anti-predator defense mechanisms in plant-associated bacteria, a library of bacteria co-isolated with their natural predator, the social amoeba *Polysphondylium pallidum*, was screened for the ability to evade amoebal predation. Results of this study showed that *Pseudomonas syringae* also secretes the lipopeptide syringafactin, which is deacylated by the amoeba. The resulting peptide derivative is detected by the bacterial sensor protein CraR (chemical radar regulator), which subsequently activates the genes *craA* and *craC*, and are responsible for converting the predator-derived signal into the amoebicidal compound pyrofactin (Fig. 3B).[63]

This feedback mechanism exemplifies how bacteria can sense and chemically respond to predation pressure and highlights the intricate chemical interplay between bacteria and their predators. Extending this concept to the rhizosphere, a highly competitive and predator-rich habitat, *Pseudomonas nunensis* 4A2e, co-isolated with its predators *P. pallidum* and the

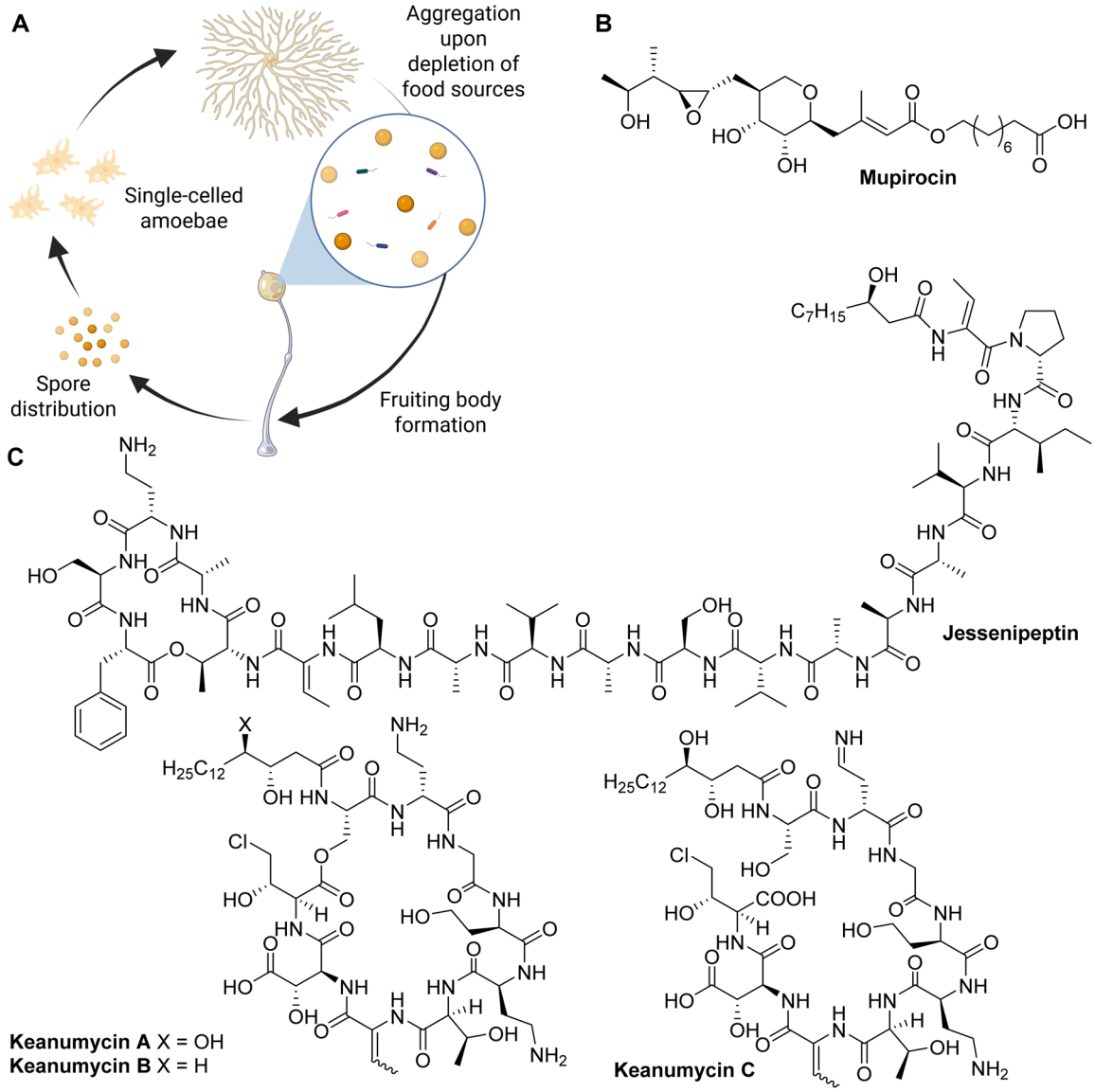

Fig. 2 (A) Simplified life cycle of *D. discoideum*. (B) Polyketide mupirocin[62] and (C) NRPs produced by the bacterium *Pseudomonas* sp. QS1027 isolated from the *D. discoideum* fruiting body-associated microbiome.

nematode *Oscheius myriophilus*, was recently characterized as a potent producer of anti-predator metabolites.

Genome mining of *P. nunensis* 4A2e revealed multiple BGCs encoding NRPS-based pathways. Subsequent chemical analyses led to the isolation and structural elucidation of the novel lipopeptides keanumycin D (amoebicidal) and nunapeptins B and C (nematodicidal).[64]

2.2 Perspective of natural products from Amoeba's microbiome

Although research on microbial communication in predator–prey interactions and the co-occurring soil microbes has intensified only recently, it has already uncovered a wealth of new chemical scaffolds, particularly peptidic ones, providing key insights into these interactions. Building on the growing understanding of these microbiomes, future research exploring the modes of action of the identified anti-infective compounds, both in amoebae and other model organisms, would be of considerable value. Similarly, investigating additional commensal members of amoebae may help to uncover the extensive, yet largely predicted and still unexplored, biosynthetic potential.

3 Examples from invertebrate microbiomes

Animals, both invertebrates or vertebrates, harbour complex communities of microorganisms, collectively known as the animal-associated microbiota, that reside both within and on their bodies.[65,66] The microbiota of a single host can comprise hundreds of taxa spanning prokaryotes, including Archaea, as well as diverse unicellular and multicellular eukaryotes and

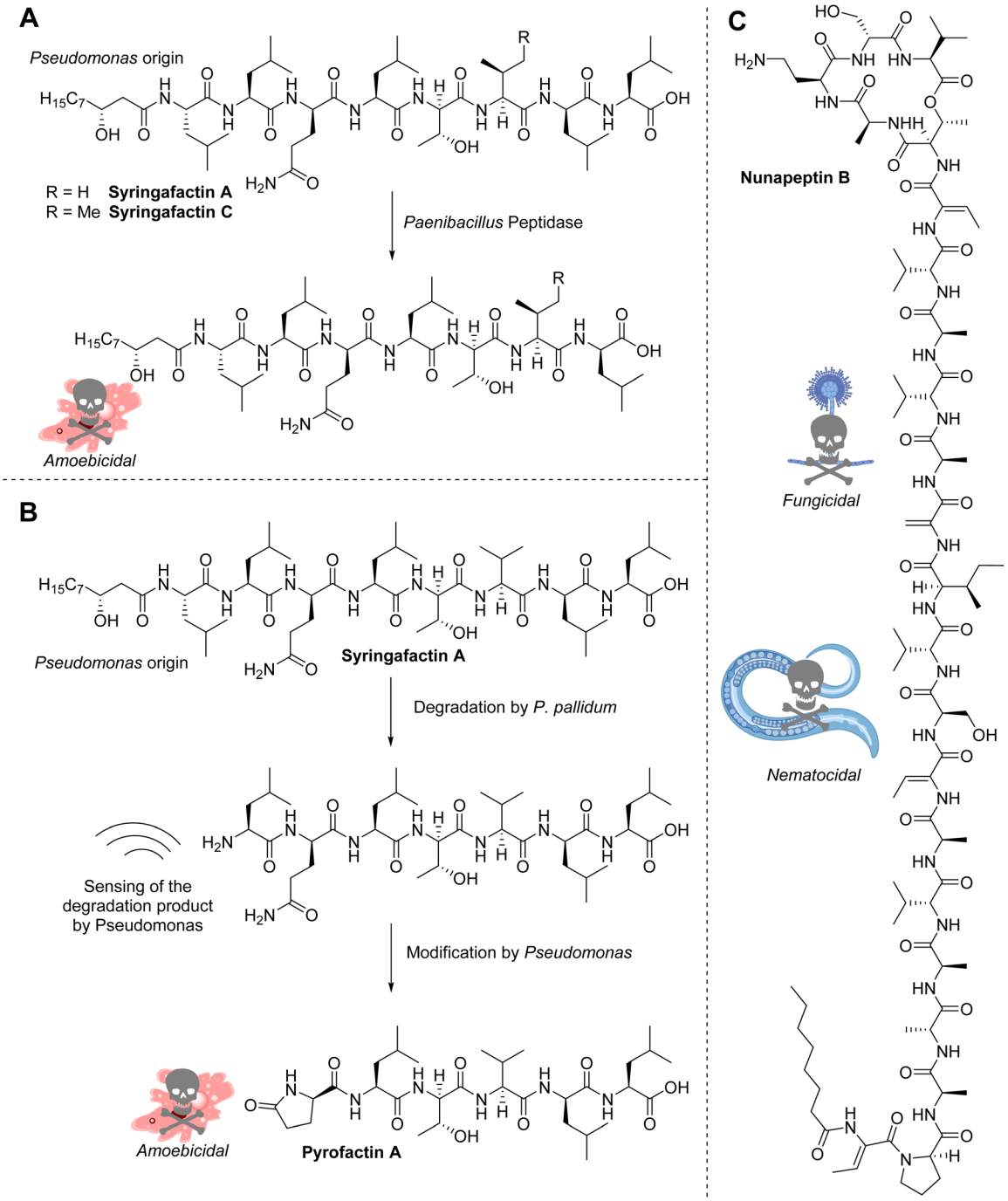

Fig. 3 Examples of natural products discovered through the study of predator–prey interactions in soil- and plant-associated microbiomes. (A) Cooperative defence against a common amoebal predator. (B) Chemical exchange of signalling molecules between a prey bacterium and its predator. (C) Nunapeptin B protects *Pseudomonas nunensis* 4A2e from nematode predation and inhibits microbial competitors in the soil.

viruses. While these microorganisms benefit from a stable and protected habitat, they reciprocally support their hosts by producing a diverse array of natural products essential for host health, physiology, and ecological stability, including compounds involved in fermentative digestion and defensive skin toxins.[67,68] Of similar importance, they also secrete immunomodulatory and protective metabolites that shape microbiome composition and function and influence disease outcomes across hosts.[69–72] In the following section, we highlight current knowledge on anti-infective and immunomodulatory compounds derived from the microbiomes of various invertebrates.

3.1 Nematodes

Nematodes host diverse and dynamic microbial communities that date back to at least the Paleozoic era,[73] and thus might have even influenced nematode evolutionary trajectories

through host-microbe co-evolutionary dynamics.[74,75] Given the extraordinary diversity of the phylum Nematoda, including free-living marine species, entomopathogens, and plant- or vertebrate-parasitic nematodes, only a few microbe–nematode relationships and their specialized metabolites have been characterized, with many more likely yet to be discovered.

3.1.1 Caenorhabditis elegans. Over evolutionary times, the *C. elegans* gut microbiota has co-evolved with its host, influencing *C. elegans* health,[76] immunity,[77] and even behaviour.[78] Meta-analyses and field sampling have also led to the establishment of a simplified yet representative model microbiome (CeMbio), comprising the twelve most abundant gut bacterial families naturally associated with *C. elegans*, and providing a versatile resource to dissect ecologically relevant host–microbiome interactions and their associated natural products.[79]

What renders *C. elegans* especially interesting in the context of functional natural product chemistry is that key members of the microbiome have been intensively analysed on genomic and metabolomic level over the past decade.

In a seminal study, Kissoyan *et al.* showed that a native *Pseudomonas lurida* strain (MYb11) from the gut of *C. elegans* biosynthesizes a cyclic lipopeptide of the viscosin family called massetolide E, which inhibits the nematicidal pathogen *Bacillus thuringiensis* (Bt) and confers protection to the host (Fig. 4).[80]

In another example, *Pseudomonas fluorescens* MYb115, a native commensal of the *C. elegans* microbiome, was identified to produces sphingolipids (SLs) that contribute to host protection during *Bt* infection.[82] Intriguingly, SLs were produced *via* a non-canonical pathway composed of an iterative PKS and a PLP-dependent serine palmitoyltransferase (SPT) homolog PfSgaB. MYb115-derived SLs do not act primarily through direct antimicrobial activity but instead reinforce host physiology by strengthening the intestinal barrier. These bacterial SLs alter host fatty acid and sphingolipid metabolism, leading to a reduction in specific sphingomyelin species compared to non-SL-producing MYb115 strains, thereby conferring protection against the Bt pathogen.

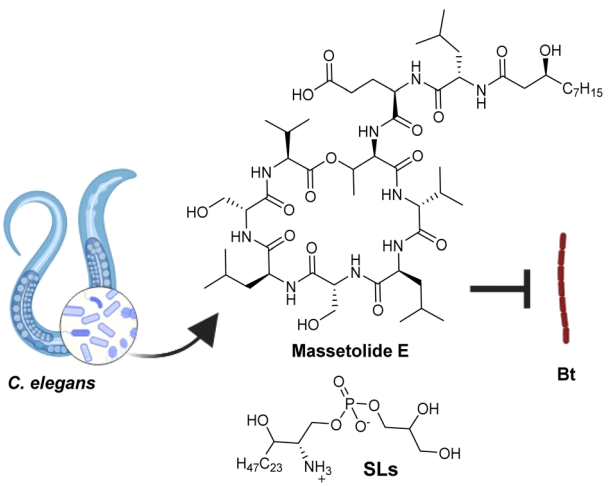

Fig. 4 Protective role of the *C. elegans* microbiota through natural product production. *Pseudomonas lurida* MYb11 produces the cyclic lipopeptide massetolide E,[81] which inhibits the nematicidal pathogen Bt and thereby protects *C. elegans*. Otherwhile members of the *C. elegans* microbiota protect their host through SL production.

3.1.2 Steinernema and Heterorhabditis. Entomopathogenic nematodes of the genera *Steinernema* and *Heterorhabditis* live in obligate symbiosis with bacteria of the genera *Xenorhabdus* and *Photorhabdus*, respectively. Together, they form an efficient insect–pathogenic complex that occupies a distinct ecological niche in soil ecosystems.[83] The infective juveniles of the nematodes carry their bacterial symbionts in their gut and actively seek out other insect as hosts. Once inside the prey insect, the bacteria are released from the nematode, rapidly multiply, and kill through the production of toxins and bioactive natural products before reproduction and release of a new generation of nematodes from the cadaver. To achieve this effectiveness, bacterial metabolites suppress not only the insect immune system,[84,85] but also prevent colonization by competing microbes,[86] and convert the cadaver into a nutrient-rich environment that supports nematode development and reproduction.[87]

Genome sequencing of the nematodes symbiont *Photorhabdus* spp. uncovered that strains allocate up to 6% of their genomes to BGCs for secondary metabolite production, a density comparable to that of prolific natural product producers such as *Streptomyces*.[88] Furthermore, a global analysis of entomopathogenic *Xenorhabdus* and *Photorhabdus* bacteria identified approximately 1000 natural product related BGCs within these taxa, which represent a unique biosynthetic and biotechnological potential,[89,90] as well as a rich source of novel natural products.[91,92] Consequently, owing to this complex interplay of pathogenesis, symbiosis, and chemical warfare, the nematode-bacterium-insect triad represents a tractable model system for studying the ecological roles and natural functions of microbial metabolites. Amid the diverse secondary metabolites produced by *Xenorhabdus* and *Photorhabdus* species, several NRPS-derived cyclic peptides and ribosomally synthesized and post-translationally modified peptides (RiPPs)[93] have been characterized for their pronounced antimicrobial and antiparasitic activities (Fig. 5).

Darobactin, a RiPP produced by *Photorhabdus khanii*, exhibits potent bactericidal activity against a range of Gram-negative pathogens, including *Escherichia coli*, *Klebsiella pneumoniae*, and *Pseudomonas aeruginosa*, by targeting the essential outer membrane protein BamA.[94] Notably, darobactin demonstrated remarkable efficacy in mouse infection models, where single or repeated doses effectively cured infections caused by multidrug-resistant strains, highlighting its promise as a lead compound for combating Gram-negative bacterial pathogens.[95] Dynobactin, another RiPP produced by *Photorhabdus australis*, inhibits Gram-negative bacteria such as *E. coli* by tightly binding the BamA lateral gate of the β-barrel assembly machinery. Notably, dynobactin A showed therapeutic efficacy in murine septicaemia and thigh infection models without detectable cytotoxicity.[96]

Among the NRPS-derived antibiotics identified, the odilorhabdins produced by *Xenorhabdus nematophila* exhibit broad-

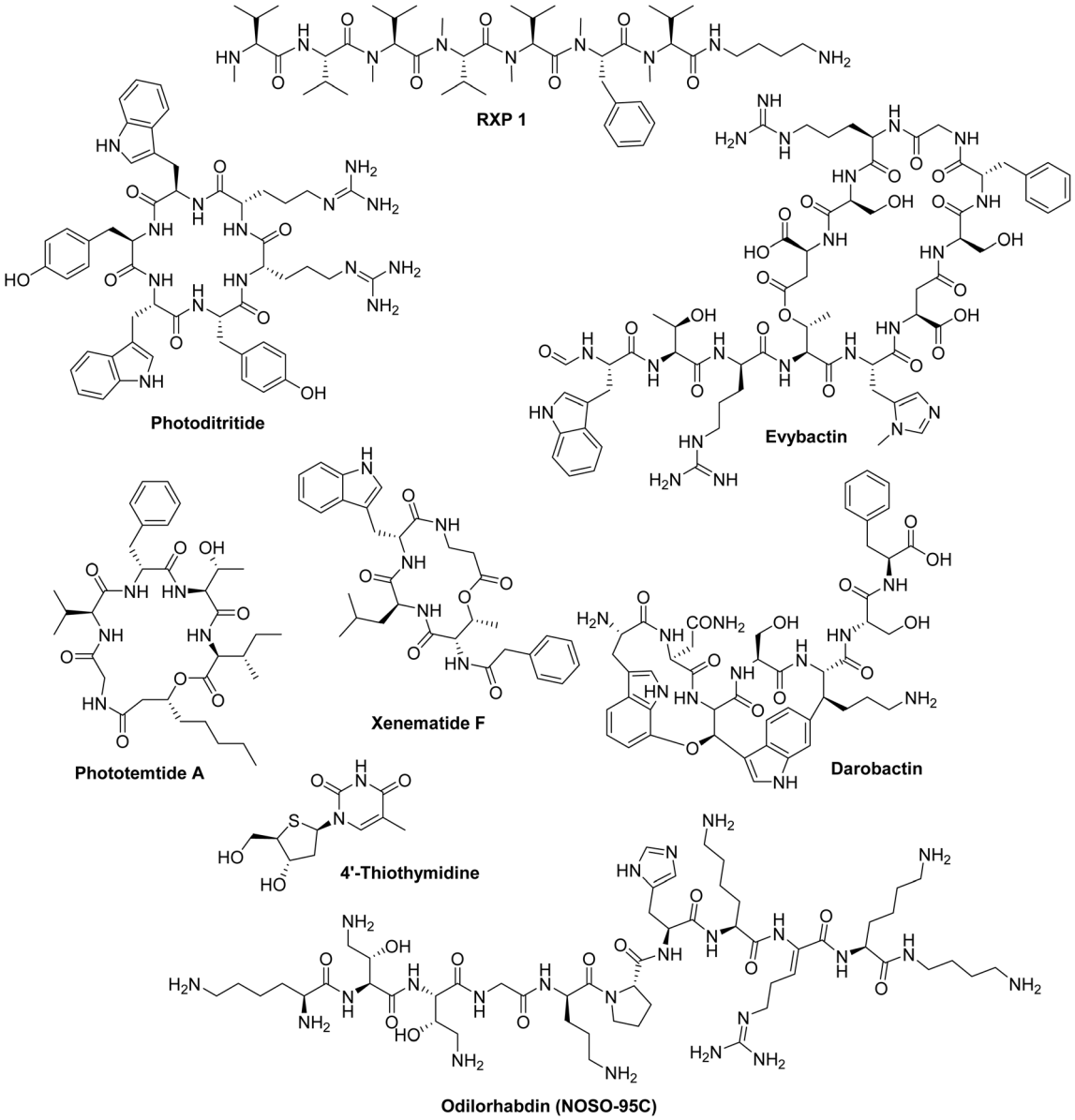

Fig. 5 Selected chemical structures of NRP and RiPP metabolites from *Xenorhabdus* and *Photorhabdus* species that have anti-infective properties.

spectrum activity against Enterobacteriaceae, including *Klebsiella pneumoniae* and *E. coli*, by inhibiting bacterial protein synthesis through binding to the 30S decoding center.[97,98] A synthetic derivative (NOSO-95179) is also bactericidal and significantly reduced pathogen burden in murine septicemia and lung infection models.

Evybactin, a cyclic depsipeptide produced by *Photorhabdus noenieputensis*, exhibits potent and selective antibacterial activity against *Mycobacterium tuberculosis* (MIC = 0.25 μg mL^{-1}) by acting as a non-quinolone binder of bacterial DNA gyrase. Remarkably, evybactin demonstrated *in vivo* efficacy, completely protecting mice from *E. coli* infection at a single dose of 100 mg kg^{-1}, while also showing no cytotoxicity towards human cell lines.[99] Along these lines, the cyclic depsipeptide xenematide F produced by *Xenorhabdus budapestensis* inhibits the growth of *P. aeruginosa*,[100] while rhabdopeptide/xenortide-like peptides (RXPs) isolated from *Xenorhabdus innexi* DSM 16336, represent a particularly potent peptide scaffold as they exhibit strong antiprotozoal activity against *Trypanosoma brucei rhodesiense* and *Plasmodium falciparum* with IC_{50} values ranging from 0.07 to 6.25 μM and 0.09 to 3.16 μM, respectively (Fig. 5).[101]

Similarly, the cyclic peptide photoditritide, obtained from *Photorhabdus temperata* Meg1 after activation of the *pdtS* NRPS gene, displays potent antibacterial activity against *Micrococcus luteus* (MIC = 3.0 μM) and moderate antiprotozoal activity against *T. brucei rhodesiense* (IC_{50} = 13 μM).[102]

Another NRPS-derived metabolite, the cyclic lipopeptide phototemtide A, together with its minor congeners phototemtides B-D, was also identified from *P. temperata* Meg1.[103] Phototemtide A exhibited weak antiprotozoal activity against *P. falciparum* (IC_{50} = 9.8 μM), highlighting the structural and functional diversity of NRPS products within these symbiotic bacteria and underscoring their potential as a source of novel antimicrobial and antiparasitic lead structures.

In addition to these peptidic metabolites, *Photorhabdus asymbiotica* KLE11370 was recently found to produce 4′-thiothymidine, an antibiotic of nucleotide rather than peptidic origin, which shows activity against clinical isolates of *K. pneumoniae*.[104]

The microbiota of other nematodes, such as the cereal cyst nematode *Heterodera filipjevi*, have also been investigated for their natural product potential. Fungal isolates obtained from this plant pathogen were found to produce a diverse range of compounds. However, none exhibited notable anti-infective activity despite extensive testing.[105,106] This observation may point toward a more specialized natural product repertoire, potentially fine-tuned to support the nematode's infection process in crop hosts.

3.2 Perspective of natural products from Nematode's microbiome

Research into the natural product chemistry of nematode-associated microbiomes has uncovered numerous bioactive compounds, including anti-infectives, while advancing the biotechnological exploration of their biosynthetic potential. Notably, the RiPP-derived darobactin has become a key focus in medicinal chemistry as a promising antimicrobial lead, while many of the other discovered NRPS-based biosynthetic gene clusters are now being further exploited in bioengineering[107] and AI-driven approaches.[108] Together, these insights position nematodes and their microbiome as a promising yet still underexplored source of anti-infective natural products and a valuable system for functional studies of both individual metabolites and microbiome members.

3.3 Insects

Insects harbour a phylogenetically diverse and chemically productive community of symbiotic microorganisms. These range from highly specialized, co-evolved symbioses,[109] where bacteria or fungi are housed in dedicated organs such as bacteriomes,[110,111] to more transient and environmentally acquired relationships on the cuticle,[112] the gut[113,114] or within nests.[115] In obligate-dependent systems, such as fungus-farming insects,[116] insect and fungal lineages have co-adapted over millions of years to maintain mutualistic exchanges: the insects cultivate fungal crops while harbouring defensive bacteria that secrete antifungal or antibacterial compounds protecting the fungal gardens from pathogens.[117,118]

Other insects, such as beetles,[119] wasps,[120] and bees, instead rely on facultative or horizontally transmitted bacteria and fungi capable of colonizing multiple niches of the insect body. Similarly, their secreted natural products function as ecological defences, protecting larvae or primary food sources from microbial pathogens by exhibiting potent antibiotic or antifungal activities.

3.3.1 Fungus-farming ants. Over the course of millions of years, fungus-farming ants have developed a complex agricultural system centred on the cultivation of a mutualistic basidiomycete fungus that serves as their primary food source.[116] This partnership is maintained through a sophisticated network of microbial and behavioural interactions, which is often described as a quadripartite symbiosis, comprising (i) the ants, (ii) their cultivated fungus (*Leucoagaricus gongylophorus* and relatives), (iii) the specialized fungal pathogens (*e.g. Escovopsis* spp. for leaf cutter ants), and (iv) defensive Actinobacteria that inhibit the growth of parasitic fungi and other microbial invaders.[121] Within this system, the ants act as both farmers and microbial stewards, maintaining a delicate balance between mutualists and pathogens through grooming, selective substrate management, and chemical defence.

Among their most important partners are filamentous Actinobacteria, primarily *Pseudonocardia*, *Streptomyces* and related genera, which colonize specialized crypts and glandular structures on the ants' cuticle,[112] but also Proteobacteria, such as members of the genus *Burkholderia*.[122] These symbionts are vertically transmitted between generations and nourished by secretions from the ants, ensuring a stable association that has coevolved with the farming lifestyle.[123,124]

Bacterial symbionts produce an array of antifungal compounds, including volatiles,[125] that suppress pathogenic fungi and other antagonistic organisms while sparing the cultivated basidiomycete (Fig. 6). Attinimicin, a member of the madurastatin-type metallophore family,[126] is produced by multiple attine ant-associated *Pseudonocardia* strains distributed throughout Central and South America and exhibits a strong binding preference for Fe^{3+}.[127] The attinimicin-Fe^{3+} complex shows no antifungal activity; however, the apo-form of the molecule suppressed the growth of different *Escovopsis* spp. and significantly reduced fungal burden in a *Candida albicans* mouse infection model. In another study, a Brazilian *Streptomyces* sp. was isolated from the microbiome of the fungus-growing ant *Cyphomyrmex* sp., which is able to biosynthesize the polyketide cyphomycin.[128] Cyphomycin showed inhibitory activity against *Escovopsis* spp. and also reduced fungal burden in a murine candidiasis model.[129] Furthermore, leaf-cutter ant associated *Streptomyces* sp. CS113 is able to produce diperamycin,[130] which has activity against MRSA and *Enterococcus seriolicida,*[131] and *Streptomyces* sp. CS149 synthesises sipanmycin A and B, which have unfortunately not been tested for any bioactivity.[132] Finally, *Burkholderia* spp., have been shown to inhibit pathogenic *Escovopsis* spp. through the production of burkholdine1213 (ref. 133) while sparing the cultivated *Leucoagaricus* fungus.[122] Interestingly, co-evolution between beneficial and pathogenic strains within the ant nest microbiome has resulted in a tit-for-tat exchange of bioactive molecules. The isolation of *Pseudonocardia* sp. ICBG1122 (dentigerumycin F) and *Escovopsis* sp. ICBG729 (conocandin B) from a *Trachymyrmex* sp. nest revealed that both strains produce natural products capable of mutually inhibiting each other's growth.[134]

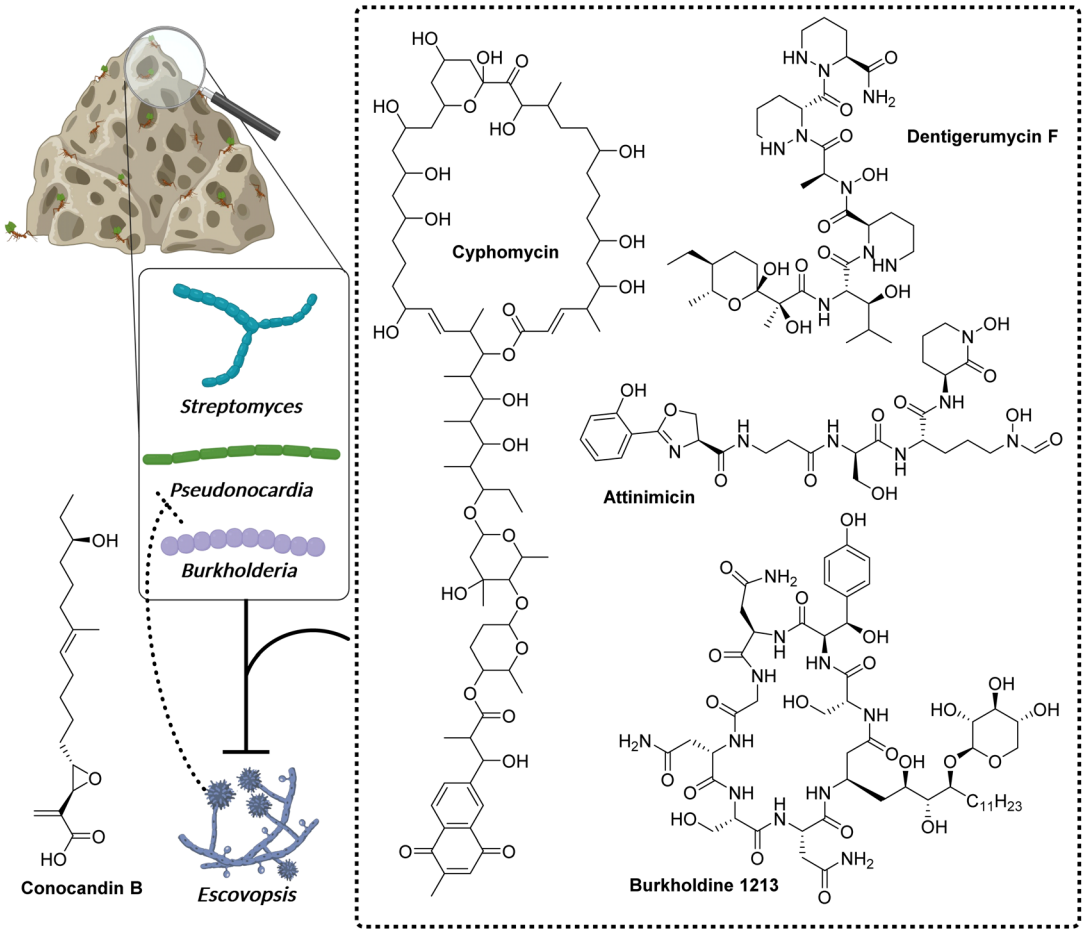

Fig. 6 Examples of bacterial genera isolated from leaf-cutting ants and their fungal garden environments, including molecules produced by beneficial microbiome members (bold rectangle) that help defend the nest against pathogenic fungi of the genus *Escovopsis*. Some *Escovopsis* spp. can counteract this chemical defence mechanism by producing antibiotic natural products of their own. An example is conocandin B, which is active against beneficial *Pseudonocardia* strains (dashed lines).

Another ecological niche explored only in recent years is that of desert-specialist fungus-growing ants from the genus *Trachymyrmex*. These ants host not only *Pseudonocardia* but also actinobacteria from the genus *Amycolatopsis*.[135] One *Amycolatopsis* sp. exhibited strong antagonism toward various contaminant fungi such as *Phoma* and *Aspergillus*, which was traced back to the production of the known antibiotic ECO-0501 (Fig. 7).[136] ECO-0501 is a polyketide synthase (PKS) type I product, which is encoded by a BGC of approximately 200 kbp, comprising multiple genes responsible for the precursor biosynthesis required for the incorporation of guanidine, glycan, and aminolevulinate moieties. ECO-0501 possessed strong antibacterial activity against a series of Gram-positive pathogens including several strains of MRSA and vancomycin-resistant Enterococci.[137]

Further studies identified an additional *Amycolatopsis* strain that produces the new antibiotic nocamycin V, which is active against *Pseudonocardia*, a genus associated with rare human infections,[138,139] and was isolated from nests of other *Trachymyrmex* species in the American Southwest as well as from other fungus-growing ants.[140] Other ant species have also been investigated for the natural product potential of their microbiomes. Unfortunately, none of the following secondary metabolites were tested for their anti-infective properties. The gut microbiomes of different carpenter ants, *Camponotus vagus*[141] and *Camponotus kiusiuensis*,[142] harboured *Streptomyces* spp. that produced diverse natural products. Lastly, *Streptomyces* sp. BA01, a gut bacterial strain isolated from the wood ant *Formica yessensis*, biosynthesized previously unknown glycosylated macrolides named formicolides.[143]

3.3.2 Fungus-farming termites. Over approximately 30 million years, termites of the subfamily *Macrotermitinae* have established a complex and highly efficient mutualism with basidiomycete fungi of the genus *Termitomyces*, which they cultivate within their nests as a primary food source.[144] The symbiosis parallels the farming systems of ants, yet evolved independently and has remained remarkably stable over evolutionary times. Chemical analyses have revealed that both the associated microbiome and the obligate microbial symbiont *Termitomyces* play not only essential roles in biomass degradation, but also produce a wide array of natural products with antimicrobial, antifungal, and other biological activities.[145–147]

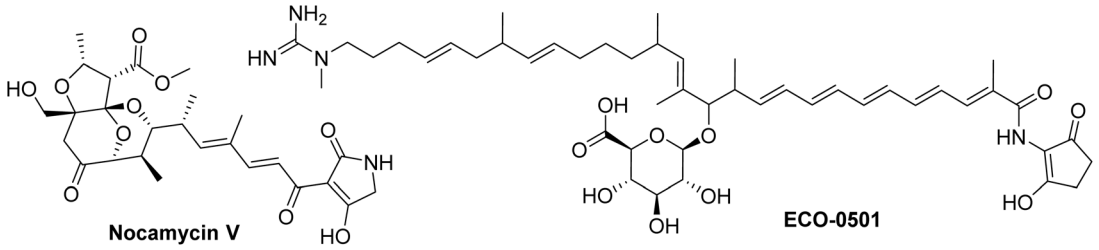

Fig. 7 Natural products isolated from the microbiome of desert-specialist fungus-growing ants.

Termitomyces have been shown to produce small polyketides and terpenes,[148] including the sesquiterpenoid alcohol drimenol,[149] which exhibits antimicrobial activity with effects against Gram-positive bacteria such as *S. aureus* and *Mycobacterium vaccae*.

Although the termite microbiota is life-stage and organ-dependent and covers a broad range of the bacterial kingdom,[150–152] much focus has been set on members of the genera *Streptomyces*,[153] *Nocardia*,[154] and *Actinomadura*,[155] as these species have demonstrated notable anti-infective potential (Fig. 8A).

Most examples yet derive from termite-associated *Streptomyces* isolates, likely due to their dominant abundance, culturability in the laboratory, and strong anti-infective activities. Just to give a few examples, pentene macrolides such as pentamycin purified from *Streptomyces* strain HF10 demonstrated strong inhibitory activity against the parasitic *Xylaria* spp. and the entomopathogen *Metarhizium anisopliae*, while exhibiting markedly lower activity towards the food fungus (Fig. 8A).[156] Similarly, *Streptomyces* sp. RB110-2, a termite-associated morphotype, produced termidomycin A, a 46-membered glycosylated macrolide exhibiting moderate antibacterial and antifungal activities against *B. subtilis*, *P. aeruginosa*, *E. coli*, and *Penicillium notatum*.[157]

From the termite-associated *Streptomyces showdoensis* BYF17, isolated from the body surface of *Odontotermes formosanus*, multiple phenazine-related metabolites including izumiphenazine A were isolated, which showed activity against *S. aureus* and *Micrococcus tetragenus*.[158] Four anthraquinone derivatives, termstrins A-D, were identified from *Streptomyces* sp. BYF63 isolated from *O. formosanus* collected in Jiangyin, China. Termstrin D showed strong antibacterial activity against *S. aureus*.[159] From *Streptomyces davaonensis* cultures also isolated from *O. formosanus*, the riboflavin analogue roseoflavin was described as a potent antibacterial compound, inhibiting Gram-positive species such as *B. subtilis* and *S. auris*.[160] A yellow pigment isolated from *Streptomyces tanashiensis* BYF-112, associated with *O. formosanus*, exhibited antibacterial activity against *M. tetragenus* and *S. aureus*.[161]

An obscurolide-type metabolite was isolated from termite-associated *Streptomyces neopeptinius* BYF101, obtained from the body surface of *O. formosanus*. This lactone-type metabolite displayed antifungal activity against the opportunistic pathogen *Cryptococcus neoformans* (MIC = 25 μg mL^{-1}).[162] In a complementary study, intestinal *Streptomyces* strains from the gut of *Macrotermes barneyi* were shown to play an equally crucial role in protecting the fungal gardens from pathogens.[156]

Additionally, member of the genus *Amycolatopsis* and *Actinomadura* have proven to be rich producers of anti-infectives. Macrotermycins, photosensitive macrolactams isolated from the *Macrotermes natalensis*-associated *Amycolatopsis* sp. M39,[163,164] exhibit potent antifungal activity specifically against the parasitic fungus *Pseudoxylaria*, highlighting a mechanism that selectively targets fungal invaders while sparing the cultivated *Termitomyces* (Fig. 8). Intriguingly, rubterolones, a class of highly substituted tropolone alkaloids,[165,166] as well as halogenated PKS-derived angucyclines,[167] were isolated from a gut-derived *Actinomadura* sp. 5–2 (RB29) associated with the termite *M. natalensis*. Although the pigments themselves showed no antibiotic activity or toxicity, their unmodified biosynthetic precursors (*e.g.* maduralactomycin A) exhibited strong but non-selective antibiotic activity. An *M. natalensis*-associated *Micromonospora* strain, which showed antimicrobial properties within co-culture, yielded new derivatives of the pyrrolomycin family, of which pyrrolomycin L showed activity against *S. aureus*.[168]

Together, these metabolites form a multilayered chemical defense network that protects the fungal cultivar *Termitomyces* from antagonists such as the co-evolved parasitic fungus *Xylaria,*[169,170] while also supporting the insect colony through microbial biosynthesis and biomass degradation. The fungus-farming termite system thus exemplifies a co-evolved, chemically mediated symbiosis in which mutualism, nutrition, and defense are tightly interwoven, sustaining one of nature's most successful forms of cooperative agriculture and serving as a rich source of novel anti-infective chemical scaffolds.

3.3.3 Beetles. Beetles (*Coleoptera*) represent Earth's most species-rich animal order, displaying exceptional morphological and physiological diversity that allows them to thrive across nearly all terrestrial and freshwater ecosystems.[119] Their evolutionary success is closely intertwined with associations to symbiotic microorganisms,[171] particularly bacteria and fungi, which occupy a range of ecological niches within and on their hosts.[172] These microbiome members contribute critically to beetle development,[173] digestion,[174] and defence,[175] often residing in specialized organs[176] or within the digestive tract.[177] Importantly, natural products play a central role in mediating these symbioses. They can function as antimicrobial defences,[178,179] signalling molecules,[180] or nutritional supplements,[181,182] thereby enhancing beetle fitness. The diversity of these chemical interactions underscores how the microbiome and the corresponding metabolism have co-evolved to underpin the ecological versatility and adaptivity of beetles (Fig. 9).[183,184]

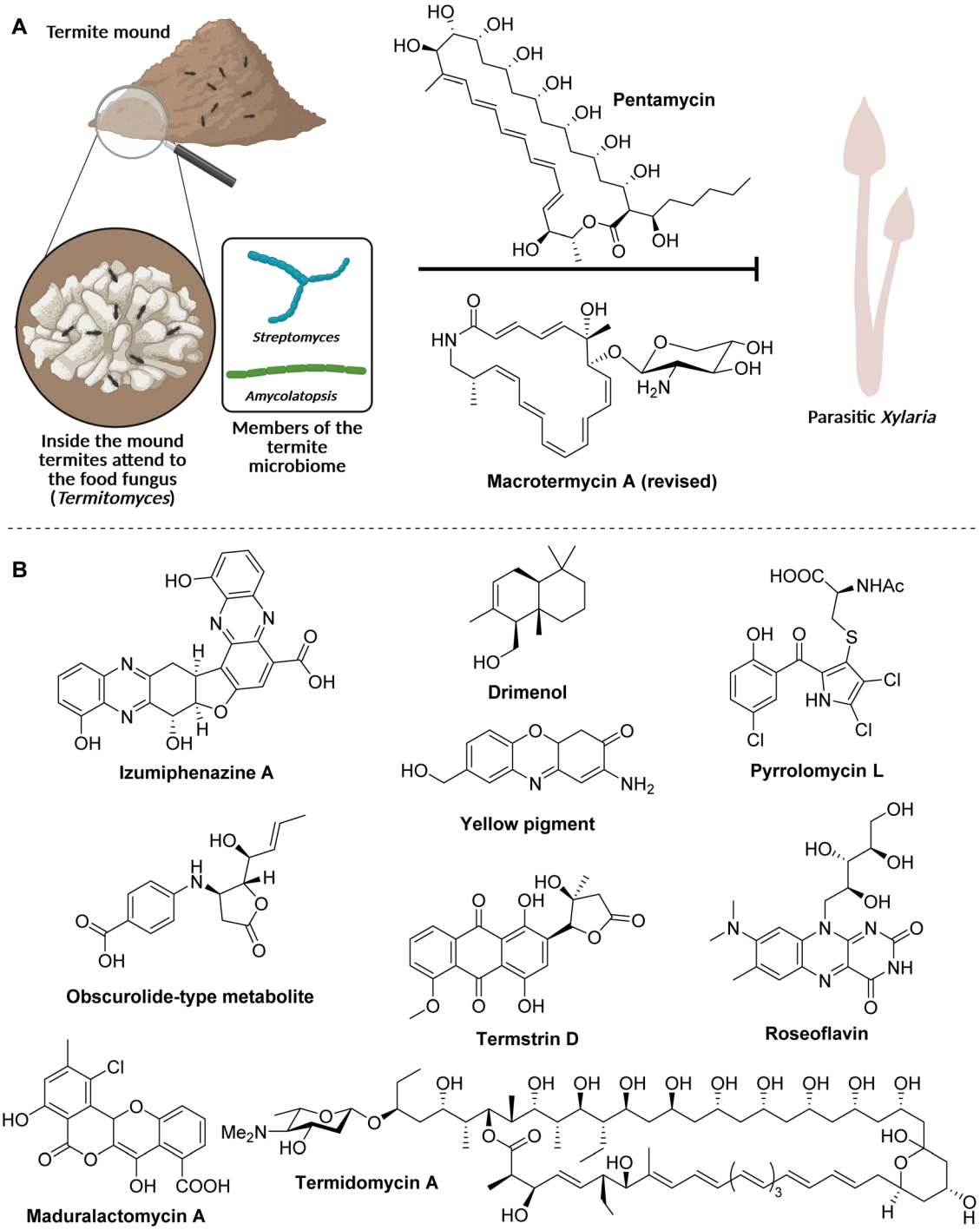

Fig. 8 (A) Members of the termite's microbiome contribute to the defence of termite fungal gardens against parasitic fungi by production of antifungal-acting natural products. (B) Chemical structures of anti-infective natural products isolated from bacterial and fungal members of the termite's microbiome.

A compelling illustration of how exploring the microbiome of insects can yield pharmacologically valuable natural products is the discovery of arenicolides from a *Micromonospora* strain isolated from the gut of the black oil beetle (*Meloe proscarabaeus*).[185] Chemical investigation of this gut-associated actinobacterium, *Micromonospora* sp. GR10, led to the identification of eight new macrolides, designated arenicolides D-K, along with arenicolide A, a previously known compound (Fig. 9). Bioassays revealed potent antimicrobial activity against multidrug-resistant and extensively drug-resistant *M. tuberculosis*. Mechanistic studies demonstrated that arenicolide A causes ATP depletion and cell wall destabilization in *M. tuberculosis*, effectively inhibiting bacterial growth. Moreover, arenicolide A retained its efficacy in macrophage infection

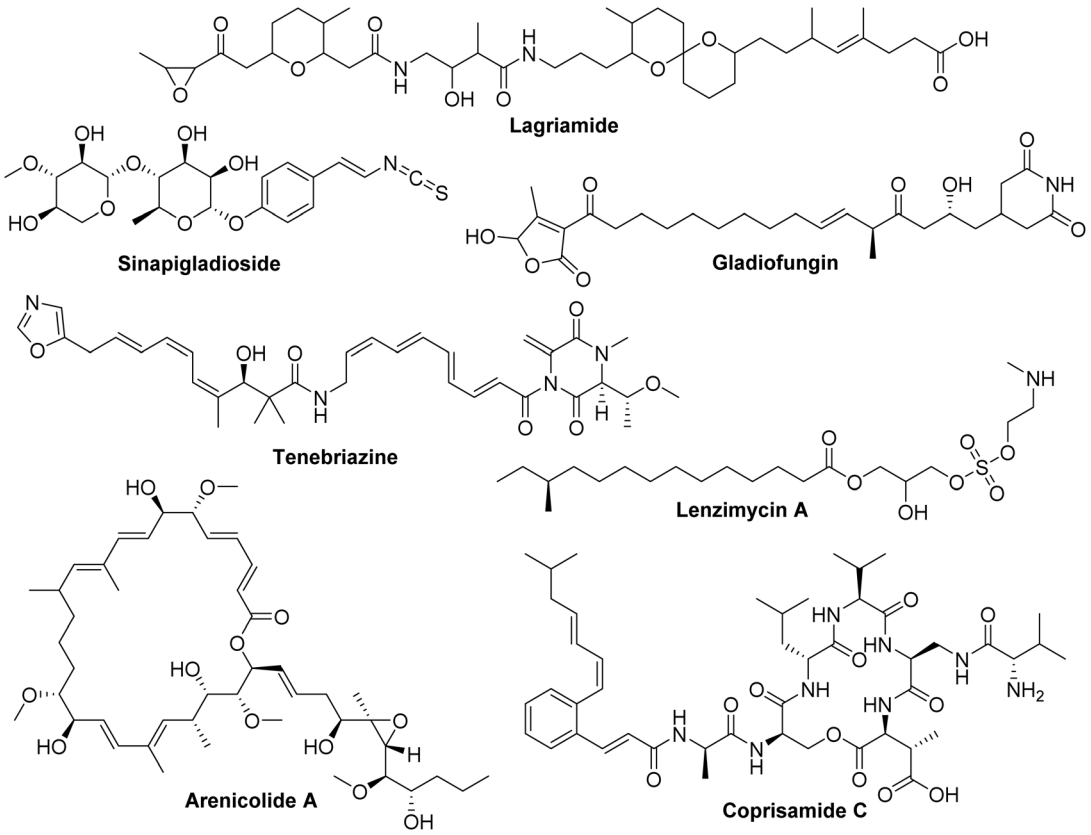

Fig. 9 Natural products isolated from the microbiome of different beetle species that have anti-infective properties.

models underscoring its potential as a new anti-tuberculosis lead compound. In another example, the beetle *Lagria villosa* maintains a stable association with the bacterium *Burkholderia gladioli* Lv-StB, which produces the hybrid PKS-NRPSs-derived lagriamide.[175] This compound occurs naturally on the eggs and in the accessory glands of female beetles, where it protects the offspring against fungal antagonists such as *Purpureocillium lilacinum*, which is also an opportunistic human pathogen.[186] The same bacterium, *B. gladioli*, that produces lagriamide in *L. villosa* beetles also synthesizes the gladiofungins, a family of cryptic glutarimide-containing polyketides uncovered through genome mining.[187] These metabolites possess potent antifungal activity against the entomopathogen *P. lilacinum*, which is a major natural threat to beetle eggs and is also an opportunistic human pathogen, as well as *P. notatum*. In addition, the same bacterial symbiont produces sinapigladioside, an antifungal isothiocyanate that is particularly active against *A. fumigatus* and is also spread onto the eggs by female beetles to protect their offspring from pathogenic fungi.[178] From the gut of the mealworm *Tenebrio molitor* (a species of darkling beetle), a *Streptomyces* sp. strain (GG23) yielded the yellow amorphous metabolite tenebriazine.[188] This compound exhibited moderate antifungal activity against *C. albicans* (MIC = 8 μg mL^{-1}) and *Trichophyton rubrum* and *Trichophyton mentagrophytes* (MIC = 16 μg mL^{-1}). From the gut of the carrion beetle *Silpha perforata*, the actinobacterial symbiont *Micromonospora* sp. UTJ3 yielded the cyclic depsipeptides coprisamides C and D, structural analogues of coprisamides A and B[189] that feature a 2-alkenylcinnamic acid unit and the unusual amino acids β-methylaspartic acid and 2,3-diaminopropanoic acid.[190] Although coprisamide C showed only weak inhibitory activity against *M. tuberculosis*, its discovery extends the structural diversity of beetle-associated *Micromonospora* metabolites and highlights the potential of carrion beetle gut microbiota as a reservoir for chemically distinct anti-infective scaffolds.

Finally, from the dung beetle *Onthophagus lenzii*, the bacterium *Brevibacillus* sp. PTH23 was isolated and found to produce lenzimycins A and B, two structurally unusual antibiotics composed of a 12-methyltetradecanoic acid-glycerol-sulfate-*N*-methyl ethanolamine framework.[191] These metabolites exhibited potent inhibitory activity against entomopathogenic *Bacillus thuringiensis* and also suppressed the growth of clinically relevant *Enterococcus faecium* and *E. faecalis* strains. Mechanistic studies indicated that lenzimycins compromise bacterial cell envelope integrity and its activity was synergistic with the activity of the peptidoglycan biosynthesis inhibitor vancomycin suggesting a different, yet unknown mode of action for the lenzimycins in a narrow spectrum of pathogens. Collectively, these results showcase that investigating beetle-associated bacteria also represent a promising strategy for the discovery of novel natural antibiotics, and highlight the pharmaceutical potential of lenzimycins. However, more in depth mode of action studies are again required to substantiate the findings and elaborate on their potential for further synergistic developments.

3.3.4 Bees and wasps. Other promising reservoirs of anti-infective metabolites are symbiotic microorganisms and microbiome members associated with flying social insects, such as honeybees and social wasps, which often live in dense colonies where the risk of pathogen transmission is high.[113] Honeybees and social wasps harbour remarkably stable yet taxonomically streamlined gut microbiomes that are intimately linked to their social lifestyle and specialized diets and transmitted through social contact.

In honeybees, this community is composed of a few conserved bacterial lineages (*e.g. Gilliamella*, *Snodgrassella*, *Lactobacillus*, *Bifidobacterium*, and *Bombilactobacillus*) that have co-evolved with their hosts for tens of millions of years.[192–194] In contrast, comparative microbiome studies of honey-feeding wasps have revealed that their microbiomes have independently converged toward those of social bees, emphasizing the selective pressures imposed by communal nesting and a sugar-rich diet.[195] Genomic analyses indicate that their microbiomes encode BGCs for different natural product classes,[196] and thus likely provide, *e.g.*, defensive and immunomodulatory[197] functions, which collectively enhance colony health and resilience.

Notably, Actinobacteria are among the reported microbial partners of bee and wasp species, likely due to their enormous capacity to produce diverse antibacterial and antifungal compounds that protect these social insects from pathogen invasion.[198] These include in particular natural products discovered from a *Streptomyces* strain isolated from mud dauber wasps, such as polyketide δ-lactone phoslactomycins, tetrahydrofuran-containing cyclolactomycins, and γ-lactone isocyclolactomycins A–C (Fig. 10), with phoslactomycins exhibiting antifungal activity against several plant fungal pathogens such as Fusarium with MIC values in the lower μM range.[199] In another study, the investigation of a mud dauber wasp nest-associated fungus, *Penicillium* sp., led to the identification of several new and known bianthrones, collectively termed neobulgarones, which also showed antifungal activity against a wasp nest-derived fungal co-isolate.[200]

Streptomyces sp. ICBG1318 isolated from the stingless bee *Melipona scutellaris* microbiota yielded the natural product meliponamycin A, a cyclic hexadepsipeptide exhibiting potent antibacterial (*S. aureus* MIC = 1.72 μg mL^{-1}) and antiprotozoal activities (*Leishmania infantum* EC_{50} = 2.2 μM).[201] Another *Streptomyces* sp. was isolated from pollen stores of the honey bee *Apis mellifera* microbiota and yielded a natural product likely representing an isomer of piceamycin,[202] a macrocyclic polyene lactam with potent inhibitory activity (MIC = 48 nM) against *Paenibacillus larvae*, the causative agent of American foulbrood, and weak activity against *E. coli* (MIC = 6 μM).[203] Overall, these examples collectively suggest that the gut microbiota of flying social insects represents a chemically rich and evolutionarily refined source of bioactive natural products, with largely untapped potential for the discovery of novel anti-infective agents.

3.3.5 Miscellaneous insects. Members of the microbiomes of other insect groups, such as grasshoppers[204,205] and moths,[206] have also been isolated and investigated for their biosynthetic potential. However, most of these studies did not include comprehensive evaluations of anti-infective properties, or the range of tested pathogens was too limited to draw meaningful conclusions.

One of the few examples showing antibacterial activity is streptoxamine, a benzoisoindole-deferoxamine hybrid isolated from a *Streptomyces* sp. associated with a locust (Fig. 11).[207] Streptoxamine exhibited weak antibacterial activity against *S. aureus* and *Mycobacterium smegmatis*, likely due to its siderophore-like properties that restrict iron uptake in these bacteria. The microbiome of the *Anopheles* mosquito, which serves as a host for the *Plasmodium* parasite,[208] includes a *Serratia* species that produces antimicrobial lipodepsipeptides known as stephensiolides (A–K).[209] These compounds, tested as a mixture, were found to inhibit the growth of *B. subtilis* and *P. falciparum*. Similarly, a systematic analysis of members of the Mosquito microbiome, uncovered a high abundance of encoded iron-binding siderophores. Among these, serratiochelin A

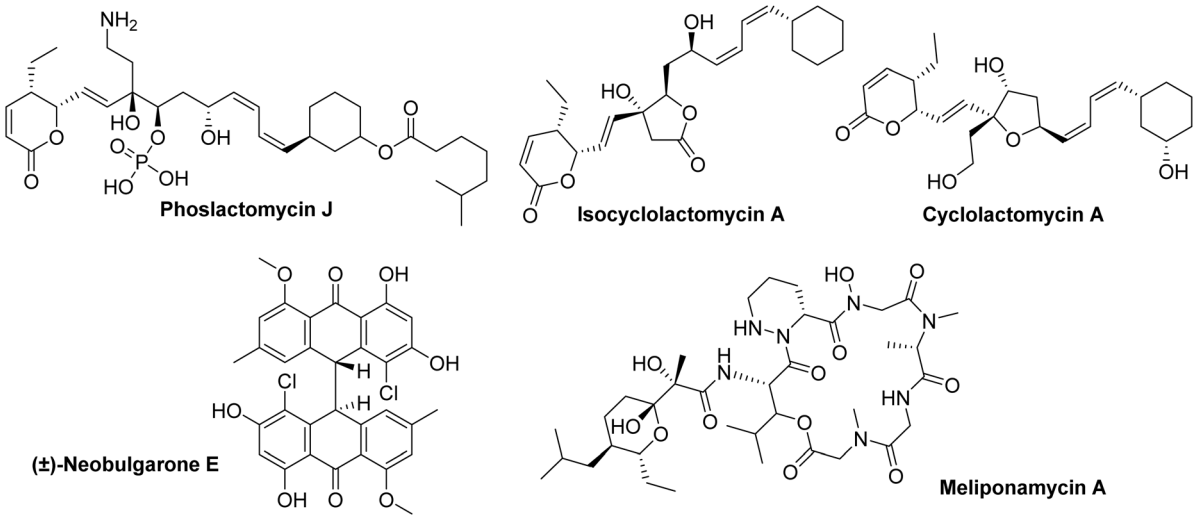

Fig. 10 Examples of new natural products isolated from the microbiome of different social flying insects that have antifungal properties.

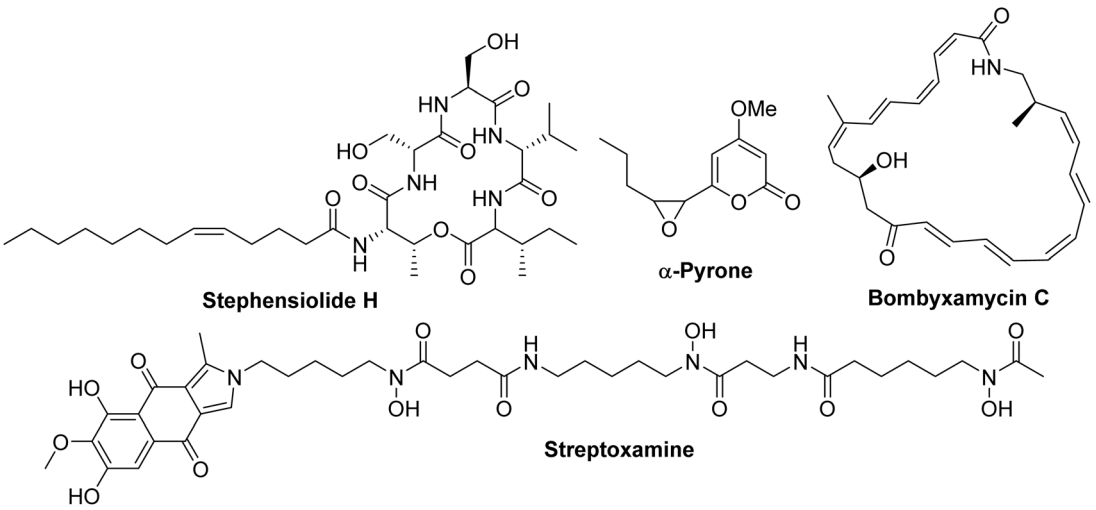

Fig. 11 Examples of natural products isolated from the microbiome of miscellaneous insects that have anti-infective properties.

and pyochelin were found to reduce female *Anopheles gambiae* overall fecundity likely by lowering their blood-feeding rate. Serratiochelin A and pyochelin were further found to inhibit the *Plasmodium* parasite asexual blood and liver stages *in vitro*.[210]

Investigation of the gut microbiota of the fly *Hermetia illucens* yielded a fungal isolate of *Chrysosporium multifidum*. Chemical analysis of its broth culture led to the identification of an α-pyrone derivative that displayed moderate activity (MIC = 62.5 μg mL^{-1}) against MRSA. These findings highlight the potential of *H. illucens*-associated fungi as a source of novel antimicrobial metabolites and suggest a possible symbiotic mechanism contributing to the larvae's resistance to ingested pathogens.[211]

Similarly, cultivation of *Streptomyces* sp. SD53 isolated from the gut of the silkworm *Bombyx mori* yielded the macrolactam natural product bombyxamycin C, which exhibited only weak antibacterial activity against the Gram-negative pathogens *Providencia hauseri* and *Salmonella enterica* as well as the Gram-positive pathogen *E. faecium*, yet further underscores the chemical diversity of insect-associated microbiota strains as reservoirs of structurally distinct metabolites.[212]

3.4 Perspective on insect microbiomes

Collectively, decades of ecology-driven research have repeatedly shown that insect-associated microbiomes represent a rich source of antibiotics and other bioactive natural products. While effective in identifying new microbial space and thus richness of unique BGCs, most research efforts have largely focused on chemical ecology and protective symbioses aspects with limited emphasis on in-depth pharmaceutical evaluation and standardized MIC reports. Despite the immense progress in identifying anti-infective metabolites using ecology-driven strategies, further translation of these findings has been constrained in most studies by limited access of metabolites, focus on ecology-guided bioactivity screening, low genetic tractability of model organisms and consequently limited efforts in understanding of their modes of action. Systematic and broad bioactivity screening of identified metabolites that also include cellular toxicity evaluations, alongside mode of action studies, may therefore uncover new anti-infective lead structures that warrant further in-depth investigation.

4 Non-human vertebrate microbiomes

Birds

Avian microbiomes are compelling targets for anti-infective natural product discovery. A recent shotgun-metagenomic survey study of migratory birds (*Anser anser*, *Anser cygnoides*, *Anser fabalis*, *Anser indicus*, *Ardea alba*, *Cygnus cygnus*, *Grus grus*, *Tadorna ferruginea*, *Tadorna tadorna*, *Tringa nebularia*) revealed exceptionally rich resistomes, with over 1000 distinct ARGs spanning ~200 resistance types.[21] These ARGs confer resistance to antibiotics such as tetracyclines and aminoglycosides and are often co-located with mobile genetic elements, frequently of proteobacterial origin. Their abundance suggests potentially elevated antibiotic exposure in the avian gut, where microbes may produce antibacterial compounds, counteract competitors' antibiotics, or respond to ingested antibiotics. Network analyses identifying ARG hubs further support the presence of strong antimicrobial pressure. Coupled with the birds' ecology, which is characterized by high mobility, diverse diets, and frequent contact with human-impacted environments, these findings suggest that avian microbiota not only disseminate antibiotic resistance but also harbour biosynthetic capacities worth exploring for novel antimicrobial scaffolds.[213] Despite growing evidence direct chemical validation has remained scarce with only few notable exceptions. One is the discovery of enteropeptin A from the commensal *Enterococcus cecorum*,[214] a member of the chicken gut microbiota (Fig. 12). This RiPP natural product intriguingly inhibits the growth of its own producer strain at micromolar concentrations.[215]

Another example is the microbiome-driven study of the uropygial gland (UG) of the toxic New Guinean bird *Pachycephala schlegelii*.[216] The UG is a specialized secretory organ at the base of the tail that produces an odoriferous, antimicrobial

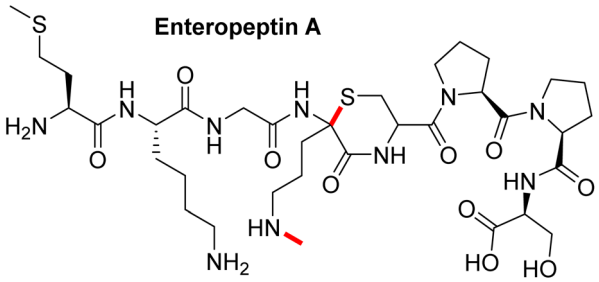

Fig. 12 RiPP produced by a bacterium isolated from the chicken gut microbiome. Posttranslational modifications are marked in red.

preen oil essential for feather maintenance[217] and protection against pathogens.[218] Amplicon sequencing uncovered a dedicated microbiome across species, and isolation of microbiome members let to the isolation of an *Amycolatopsis* species, amongst others, which exhibited strong inhibitory activity against keratinolytic feather-degrading bacterial and fungal pathogens.[219]

Chemical analysis of the strain revealed the production of both, known antibiotics, including rifamycin congeners exhibiting strong antibacterial activity, the antifungal macrolactam ciromicin A, and two novel families of NRPs with distinctive structural features. These newly identified metabolites, named pachycephalamides and demiguisin, were also detected directly in feather extracts, confirming their ecological relevance (Fig. 13). The surface-active pachycephalamides exhibited antibacterial activity against *E. coli*, *P. aeruginosa*, *E. faecalis*, *M. vaccae*, and *P. notatum*, whereas demiguisin showed no activity against any of the tested bacterial or fungal strains. Interestingly, a combination of pachycephalamides and demiguisin displayed activity against *C. albicans*, suggesting a synergistic effect between the two compound classes. Overall, this study highlights the UG microbiome as a previously overlooked niche for natural product discovery.

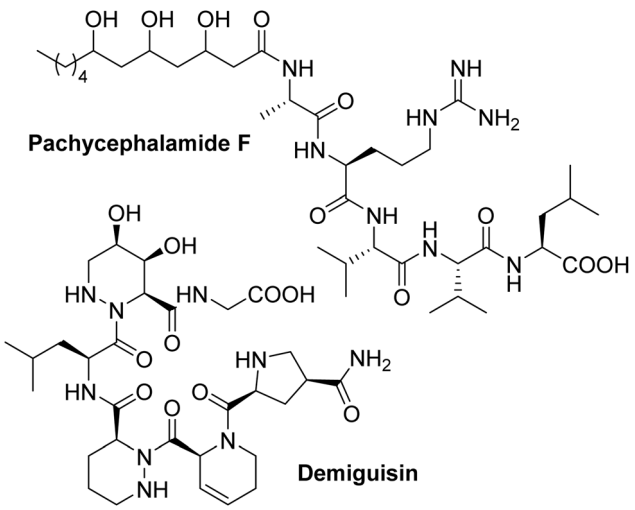

Fig. 13 Natural products produced by the microbiome member *Amycolatopsis* sp. PS_44_ISF1 isolated from the UG of the New Guinean toxic bird *P. schlegelii*.

4.1 Mice

Mice are the most widely used model organisms for studying human physiology and disease, yet the natural product repertoire of their microbiota, and their functions, remain surprisingly underexplored, resulting in a yet very rudimentary molecular understanding of potentially protective or harmful microbe-host interactions.[220] A recent genome mining-based study uncovered a cryptic NRPS biosynthetic gene cluster in the genome of *Bacillus cereus* DSM 28590, isolated from the mouse intestine,[221] predicted to produce a thiazole-containing metabolite. This cluster was captured using *Direct Pathway Cloning*[222] and heterologously expressed in *E. coli*, leading to the production and identification of bacillamide D (Fig. 14).[223] While the natural product had no antibacterial properties, bacillamide D was found to be a potent cytotoxin, inhibiting proliferation and migration of human and murine intestinal cells as well as primary organoids *in vitro*.

In another study, the intestinal fungus *Fusarium* sp. LE06, isolated from the murine gut *via* bioactivity-guided screening, produced two previously undescribed glycosides, fusintespyrone A and cerevisterolside A, both with distinctive structural features.[224] Fusintespyrone A contains a rare 4-deoxy-glucose moiety linked to a polyketide fragment, while cerevisterolside A represents a novel sterol glycoside with the sugar attached at the C-17 position of the sterol backbone. Biologically, fusintespyrone A showed pronounced antifungal activity against *A. fumigatus*, *Fusarium oxysporum*, and *Verticillium dahliae* with MIC values ranging between 1.56 and 6.25 μg mL^{-1}.

4.1.1 Immunomodulatory metabolites. Driven by the rapid expansion of microbiome research in murine disease models, a growing body of evidence has revealed that lipids produced by the gut microbiome play a significant role in

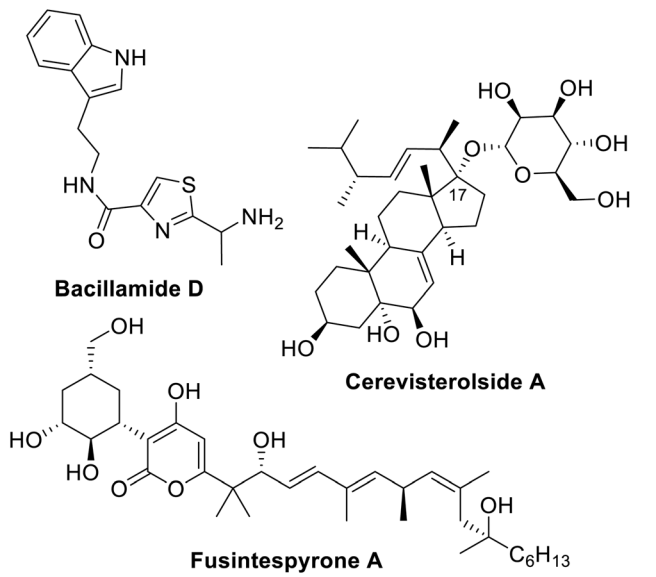

Fig. 14 Natural products produced by members of the murine gut microbiota.

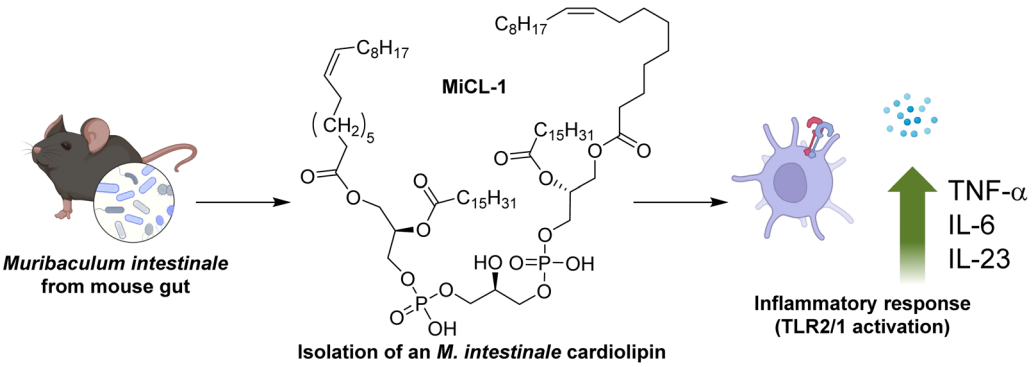

Fig. 15 Cardiolipin MiCL-1 induces a proinflammatory response by activating the TLR2/1 heterodimer receptor complex on murine dendritic cells.

shaping host immunity by influencing processes such as inflammation, immune cell differentiation, and host-microbe interactions.

In particular, the strictly anaerobic gut bacterium *Muribaculum intestinale* has been shown to elicit adaptive immune responses during immune homeostasis.[225] A bioassay-guided fractionation of a bacterial extract of *M. intestinale* using murine dendritic cells uncovered a lipid metabolite, designated MiCL-1 (Fig. 15).[226] MiCL-1 was structurally characterized as an 18 : 1–16 : 0 cardiolipin, a lipid class typically enriched on concave membrane surfaces in both bacterial and mammalian systems. Functionally, MiCL-1 potently induces the production of pro-inflammatory cytokines such as tumour necrosis factor (TNF-α or just TNF), interleukin 6 (IL-6), and IL-23, without affecting the anti-inflammatory cytokine IL-10. Mechanistic investigations demonstrated that MiCL-1 activates a toll-like receptor (TLR) 2/1 heterodimer, but not TLR6, thereby promoting pro-inflammatory signalling in murine immune cells.

4.2 Miscellaneous mammals

Although bioinformatic analyses indicate that animal-associated microbiota harbour a wealth of uncharacterized BGCs, only few studies have explored the microbial diversity and biosynthetic potential of mammals beyond mice and humans.[65] For instance, a sika deer dung-derived actinomycete, *Actinocorallia aurantiaca*, was found to produce several furan-containing polyketides, although their anti-infective activities were not evaluated.[227] Similarly, an investigation of the nasal microbiome of pigs led to the expected isolation of *P. aeruginosa* strains that produced known antimicrobials such as pyoluteorin.[228] In another study, the BGC of a RiPP identified in *Streptococcus suis*, an opportunistic pathogen in pigs, was heterologously expressed, yielding suisactin, which was unfortunately not tested for its bioactive properties.[229] One notable exception is the in depth investigation of a new RiPP family found in *S. suis via* a high-throughput elicitor screening (HiTES). It was shown that Vitamin B_3 induces the production of threoglucins,[230] which are actually antibacterial at high concentrations (15–30 μM) against its own producer *S. suis* (Fig. 16).

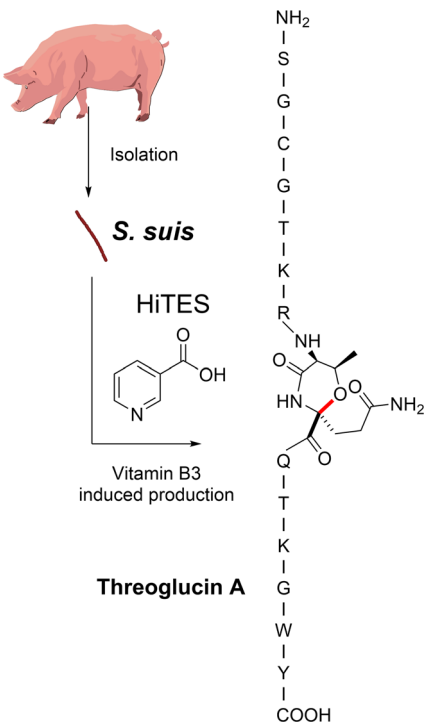

Fig. 16 Identification of a new RiPP class from *Streptococcus suis* member of the pig microbiome. Cultivation in the presence of a small-molecule library to modulate secondary metabolism, led to the discovery of threoglucin A, which feature a central cyclic ether moiety. Post-translational modifications are shown in red; amino acids are indicated using the one-letter code.

4.3 Perspectives on the exploration of non-human vertebrate microbiomes

Despite these examples, microbial secondary metabolism in non-human mammals remains largely unexplored. In particular, a deeper understanding of the secondary metabolites produced by both laboratory and wild-derived murine microbiomes could not only yield insights into host-microbe interactions but also clarify how microbial chemistry may influence the outcomes and reproducibility of mouse-based studies.[231] As microbial metabolites can profoundly modulate host biology, uncovering the breadth and function of murine microbiome-derived natural

products is essential for interpreting experimental results in mouse-studies, but also for identifying bioactive compounds with translational potential. Within a One Health framework, correlations between ARG and BGC abundances, especially in migrating animals as well as animals in captivity and livestock still remain at a mostly descriptive stage and largely unexplored with respect to the discovery of natural product scaffolds. More in depth exploration of this wealth of information alongside systematic bioactivity profiling against commensals, producer strains, and pathogens, may accelerate the targeted discovery of natural products not only of those of ecological relevance, but also promising anti-infective properties.

5 The human microbiota

Bioinformatic analyses have repeatedly demonstrated that the human microbiome, encompassing habitats such as the skin, eye, lung, gut, and oral cavity, represents a rich reservoir of BGCs, which in some cases can also be linked to different disease states.[3] Unlike most animal microbiomes, the human microbiome has been focus of intense studies within the last years, which has led to the discovery of numerous antimicrobial natural products highlighting the therapeutic potential of resident microorganisms.[232,233]

5.1 Examples from culturable bacteria

Salivabactin, a PKS-NRPS derived hybrid natural product produced by *Streptococcus salivarius* (Fig. 17) a commensal member of the human oral microbiome and probiotic, exhibits potent bactericidal activity against *Streptococcus pyogenes* (MIC ~2 μg mL^{-1}).[234] Salivabactin achieved complete eradication 12 hours after exposure at a concentration of 10× MIC, showing efficacy comparable to the clinically used antibiotic penicillin G, and induced morphological changes in treated cells relative to untreated cells. Salivabactin also displayed broad activity against other major Gram-positive pathogens including *Streptococcus agalactiae*, *Streptococcus pneumoniae*, *Streptococcus mutans*, and *Staphylococcus aureus*, but showed little effect on

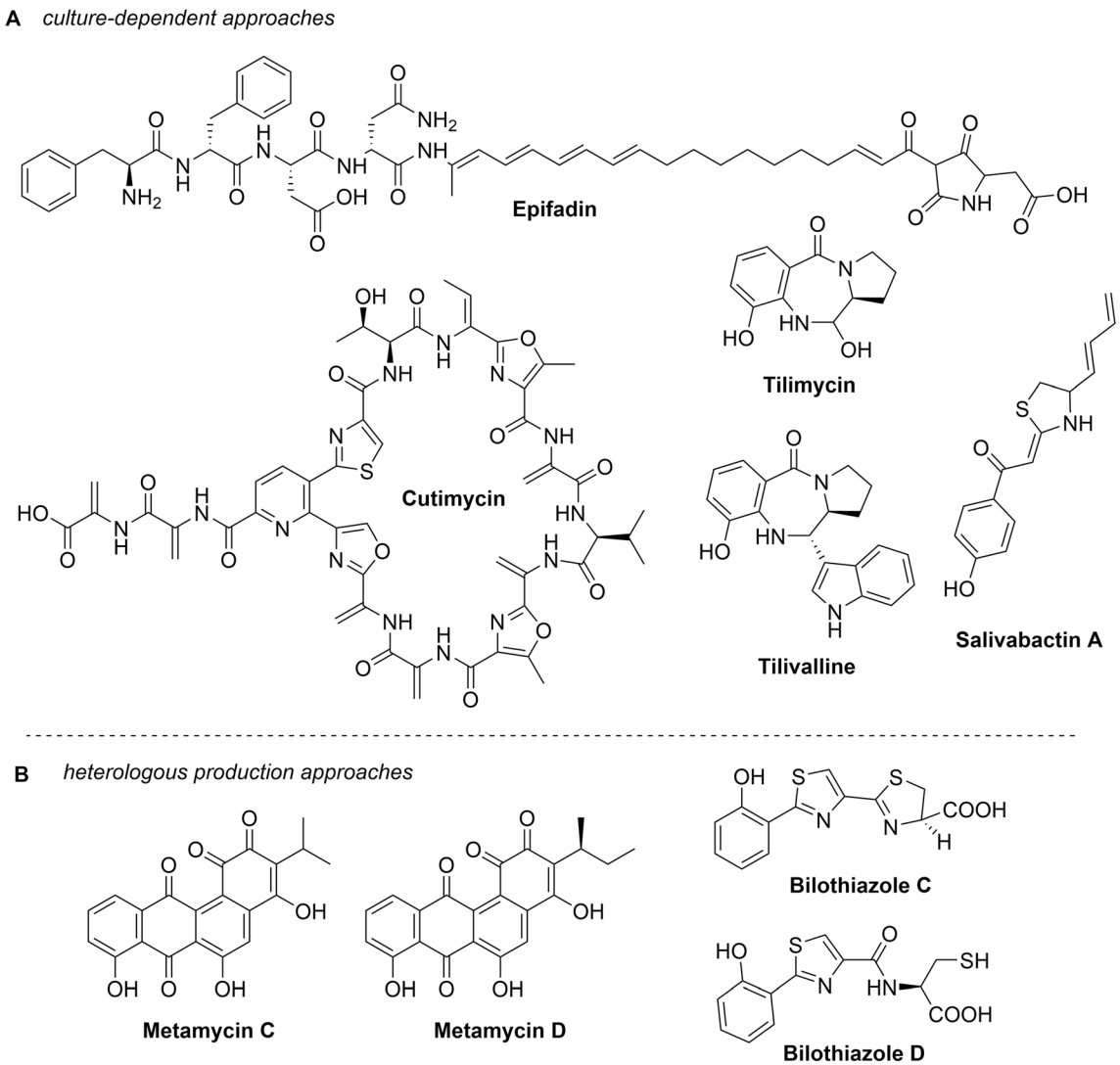

Fig. 17 Structurally diverse natural products with anti-infective properties produced by members of the human microbiota.

Gram-negative species. In a murine intramuscular infection model mimicking necrotizing myositis, a single dose of salivabactin (6 mg kg^{-1}) provided protection comparable to penicillin G (16 mg kg^{-1}), underscoring its *in vivo* efficacy against Group A Streptococcus infection.

Epifadin, a hybrid NRPS-PKS antimicrobial produced by *Staphylococcus epidermidis*, the dominant member of the human skin and nasal microbiomes, represents a unique natural product architecture combining NRPS and PKS biosynthetic logic.[235] Epifadin is highly unstable under physiological conditions but displays potent bactericidal activity against *S. aureus*, with inhibitory concentrations of 0.9–1.5 μg mL^{-1}. It exhibits broad-spectrum activity against Gram-positive bacteria, select Gram-negative species, and even yeasts, while showing low cytotoxicity toward human cells. Mechanistically, epifadin disrupts bacterial membrane integrity. In a cotton rat nasal colonization model, epifadin-producing *S. epidermidis* significantly reduced *S. aureus* burden compared with an epifadin-deficient mutant, demonstrating *in vivo* efficacy and highlighting its potential as a probiotic strategy to combat multidrug-resistant *S. aureus*.

Cutimycin, is produced by *Cutibacterium acnes*, a dominant inhabitant of the human skin and hair follicle environment.[236] It is encoded by a RiPP BGC widespread among *C. acnes* strains, and structurally belongs to the thiopeptide family. Cutimycin displays potent anti-staphylococcal activity, with MIC values of 0.2–0.8 μM against different MRSA strains and *S. epidermidis*, while sparing commensal *Actinobacteria* such as *C. acnes* and *Corynebacterium* species. It is a ribosomal inhibitor that targets bacterial protein synthesis and its production is inducible in the presence of *Staphylococcus* species. Functionally, cutimycin reshapes the follicular microbiome by increasing the *C. acnes*:*Staphylococcus* ratio *in vivo*, demonstrating its ecological role in niche competition. These findings highlight the therapeutic promise of cutimycin and its producer strains as potential microbiome-based interventions to restore healthy skin microbial balance and limit *S. aureus* colonization.

Members of the *Klebsiella oxytoca* species complex, which frequently colonize the human gut during infancy and early childhood, exemplify the dual nature of microbiota-associated secondary metabolism. These strains produce the enterotoxins tilimycin and tilivalline,[237,238] molecules long recognized for their cytotoxic potential, yet they also contribute to colonization resistance against enteric pathogens such as *Salmonella* Typhimurium. Mechanistic investigations in mouse models demonstrated that this protective effect can be mediated through a toxin-dependent pathway, in which tilimycin-driven antimicrobial activity suppresses *S. Typhimurium* overgrowth and maintains intestinal ecological balance.[239]

5.2 Example of heterologous expression approaches

A major challenge in microbiome-based natural product discovery is that a large proportion of human-associated microorganisms cannot be readily isolated or cultivated under standard laboratory conditions. Many taxa depend on highly specific environmental conditions, such as strict anaerobiosis, host-derived nutrients or interspecies chemical cues, that are difficult to reproduce *in vitro*.[28,30] Consequently, the biosynthetic potential remains largely inaccessible to classical cultivation approaches and can instead be accessed through heterologous expression in suitable hosts. An example of this approach is the discovery of metamycins C and D, natural products identified from a BGC detected in human oral metagenomes.[240] Because no native bacterial isolate carrying this BGC was available, researchers employed a synthetic biology strategy to reconstruct and express it. The coding sequence of the BGC was synthesized *de novo*, codon-optimized for expression in *Streptomyces* species, and assembled into an *E. coli-Streptomyces-yeast* shuttle vector for chromosomal integration into *Streptomyces albus*.

Heterologous expression of the synthetic BGC construct yielded distinct metabolites absent in control strains, which were identified as metamycins C and D. These compounds displayed strong antimicrobial activity against several Gram-positive oral commensals and opportunistic pathogens, including *Streptococcus*, *Atopobium*, *Actinomyces*, *Rothia*, and *Corynebacterium* species, with potency comparable to that of tetracycline. Importantly, the BGC is actively transcribed in human supragingival plaque during early biofilm formation, suggesting that metamycins C and D may contribute to niche competition and microbial balance within the oral cavity. This case exemplifies how metagenomic reconstruction and heterologous expression can uncover previously inaccessible microbiome-derived natural products with ecological and therapeutic relevance.

Another example is the discovery of bilothiazoles, a family of yersiniabactin-type metallophores[126] identified from a BGC originating from an uncultured *Bilophila* strain of the human gut microbiome.[241] Because the native producer could not be isolated, a synthetic biology approach involving gene synthesis, and heterologous expression experiments was employed to reconstruct the BGC and produce bilothiazoles. These metabolites share structural features typical of metal-binding thiazole compounds, suggesting a role in metal acquisition and interbacterial competition. Among them, bilothiazoles C and D exhibited weak antibacterial activity against *B. subtilis* and *S. aureus*.

A plethora of metagenome mining studies have shown that the human microbiome possesses an extensive biosynthetic capacity for antimicrobial peptides, notably of RiPP origin.[3,242–245] However, efforts to isolate these compounds from their native producers often fail, as either the producer remain challenging to culture or BGCs stay silent under standard laboratory conditions. Overcoming these and other limitation and allowing their rapid evaluation and characterization has been a topic of increasing interest. The following section highlights a selected set of representative examples that illustrate recent advances in the field.

In an example reported by Bushin *et al.*, the BGC encoding the machinery responsible for the production of streptosactin (*gggA-C*) from *Streptococcus thermophilus* was redesigned and introduced into an *E. coli*-based co-expression system to generate sufficient product for detailed structural analysis and

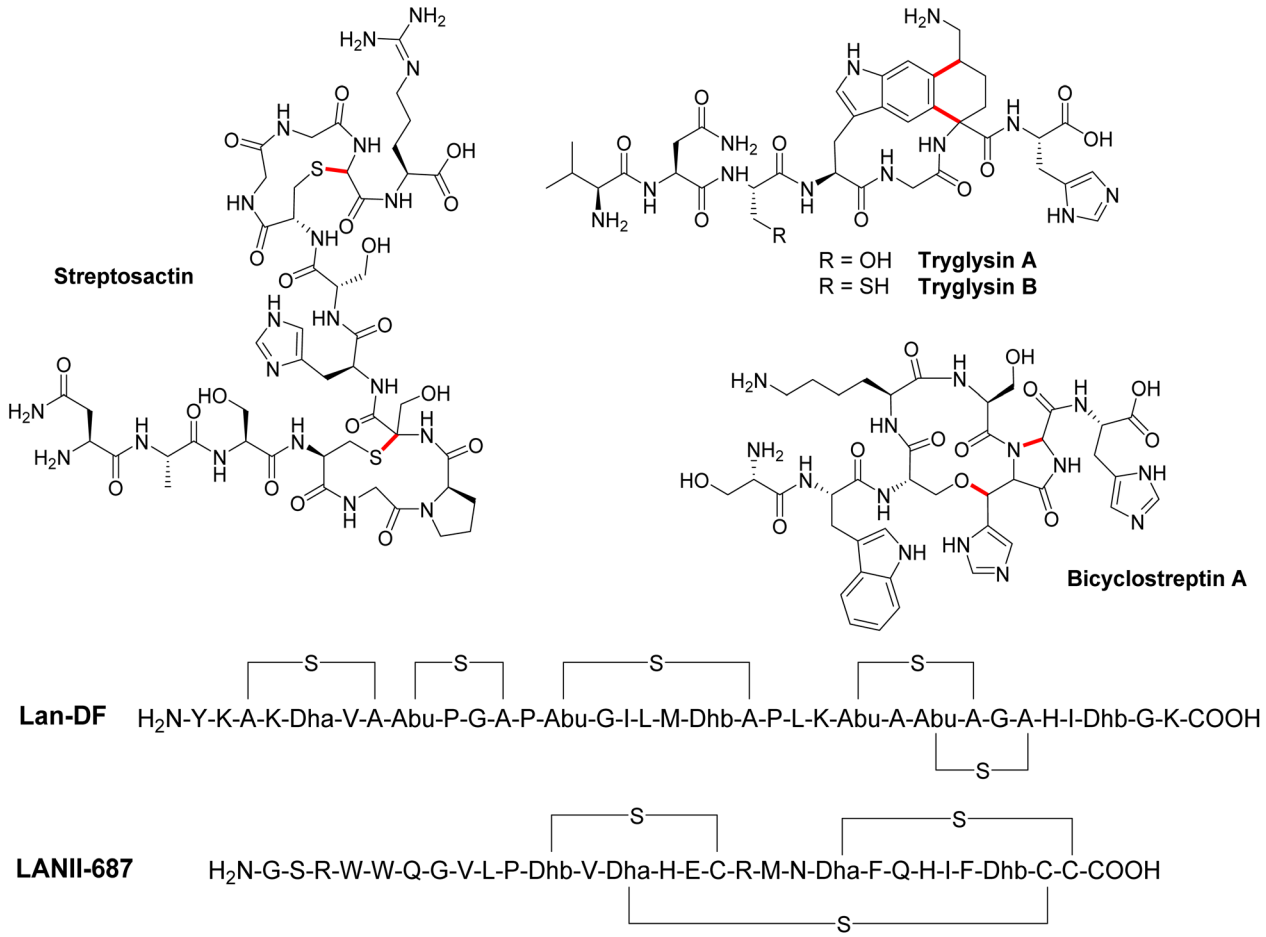

Fig. 18 RiPPs from the human microbiome showing anti-infective activity. Posttranslational modifications are marked in red. Thioether bonds are indicated in Lan-DF and LANII-687 according to the nomenclature generally accepted for lanthipeptides.[250] Abbreviations: Abu = (2*S*)-2-aminobutyric acid; Dhb = dehydrobutyrine; Dha = dehydroalanine.

bioactivity testing (Fig. 18).[246] Interestingly, streptosactin exhibits growth–inhibitory activity against its own producer strain, indicating that this RiPP functions as a fratricidal agent in *S. thermophilus*, which is a common human oral microbiome member. A similar strategy was employed to elucidate the structure and bioactivity of the tryglycins, which are RiPPs containing a unique tetrahydro[5,6]benzindole modification.[247] Whereas tryglycin A is produced by *Streptococcus ferus*, a member of the oral microbiota in various rodent species, tryglycin B is produced by *S. mutans*, which is a member of the human oral microflora. Both tryglycins exhibit potent growth–inhibitory activity against other *Streptococcus* species at nanomolar concentrations (approximately 100 nM). Finally, bicyclostreptin A, which also originates from *S. thermophilus*, features an unprecedented structural motif comprising a macrocyclic β-ether and a heterocyclic sp^3-sp^3 linkage between a backbone amide nitrogen and an adjacent α-carbon.[248] These unique modifications are installed by two radical *S*-adenosylmethionine metalloenzymes. Bicyclostreptin A exhibits antimicrobial activity against its own producer strain at low micromolar concentrations.

Ayikpoe *et al.* recently developed a scalable platform that combines high-throughput bioinformatics with automated BGC refactoring to evaluate uncharacterized RiPP BGCs in genetically tractable hosts.[251] As a proof of concept, 96 RiPP BGCs spanning diverse bacterial phyla and comprising 383 biosynthetic genes were refactored in a high-throughput manner with an overall success rate of 86%. Heterologous expression in *E. coli* enabled the identification of 30 compounds representing six RiPP classes: lanthipeptides, lasso peptides, graspetides, glycocins, linear azol(in)e-containing peptides, and thioamitides. Several lanthipeptides displayed antibacterial activity, including a class II lanthipeptide (not shown) with low-micromolar potency against the ESKAPE pathogen *Klebsiella pneumoniae*.

A systematic genome mining study of 2229 Human Microbiome Project genomes (representing bacterial species colonizing the skin, gastrointestinal tract, urogenital tract, oral cavity, and trachea) was conducted by King *et al.* to identify RiPP BGCs.[249] In total, 70 non-redundant candidates RiPPs were refactored for heterologous expression in *E. coli*, enabling the purification of 21 lanthipeptides and four lasso peptides. These RiPPs were screened against a panel of 46 bacterial strains comprising healthy human commensals, dysbiosis-associated species, and ESKAPE pathogens. Several compounds exhibited extended-spectrum activity against clinically relevant

multidrug-resistant pathogens, whereas three displayed narrow-spectrum potency against vancomycin-resistant *Enterococcus* (VRE) with minimal impact on beneficial commensal bacteria. Additional RiPPs selectively inhibited organisms associated with dysbiosis, including vaginal *Paeniclostridium sordellii* and skin *Streptococcus dysgalactiae*, or taxa linked to disruption of healthy microbial communities, such as vaginal *Lactobacillus crispatus* and nasal *Dolosigranulum pigrum*. Moreover, six nasopharynx-derived RiPPs were active against common commensal gut bacteria. Notably, among the characterized RiPPs, LANII-687, originally identified in a vaginal strain of *Lactobacillus iners*, exhibited potent antimicrobial activity against dominant members of the healthy vaginal microbiome (*Lactobacillus crispatus* (MIC = 0.15 μM), *Lactubacillus gasseri*, and *Lactobacillus jensenii*) as well as against major human pathogens, including *S. aureus*, *S. pneumoniae*, and *E. faecium*.

In studies dedicated to identifying nisin-like BGCs, the group around van der Donk applied the RODEO tool to the public RefSeq database and uncovered novel nisin-like class I lantibiotics encoded in gut microbial genomes.[252] Manual curation revealed several previously unrecognized lanthipeptide BGCs. The corresponding nisin-like clusters were codon-optimized and heterologously expressed using an enhanced lantibiotic production platform, enabling efficient peptide purification and characterization. Among these, Lan-Df, derived from *Dorea formicigenerans*, a common human gut bacterium, exhibited the most potent antimicrobial activities (MICs between 1 and 5 μM).[253] Remarkably, Lan-Df inhibited multiple clinically relevant pathogens, including *E. faecium*, *S. aureus*, *S. epidermidis*, and even the nosocomial pathogen *Clostridioides difficile*. Additionally, lantibiotic resistance genes were profiled in pathogenic and commensal strains, which in combination with structure–activity relationship analyses of the nisin-like analogues identified key regions and residues governing antimicrobial activity. Along these lines, a related study by Hourigan *et al.* uncovered novel nisin BGCs, approximately 30% of which appeared to be associated with mobile genetic elements, including clusters found in pathogenic bacteria.[254] About 107 novel nisin-like peptides were predicted of which five representatives were heterologously expressed, all displaying antimicrobial activity.

Overall, these findings underscore the immense potential of microbiome-derived RiPPs as a source of targeted antimicrobial agents and demonstrate the power of synthetic biology-driven platforms to overcome expression challenges in natural product discovery.

5.3 Immunomodulatory metabolites

Similar as shown in mice, gut microbiome-derived lipids have also been found to modulate key immune responses in humans. As one example, *S. pyogenes*, a member of the human skin and throat microbiome, also produces a cardiolipin, designated SpCL-1 (historically known as "Coley's Toxin"), which elicits a similar immunostimulatory response in humans (Fig. 19).[255] Actually, SpCL-1 and MiCL-1 differ solely in their acyl chains, with SpCL-1 containing stearic acid (18 : 0) and MiCL-1 palmitic acid (16 : 0) as the saturated lipid component. SpCL-1 activates human dendritic cells through the same TLR2/1 heterodimer-dependent signalling pathway as MiCL-1, resulting in the robust induction of pro-inflammatory cytokines TNF-α, IL-6, and strong stimulation of IL-23 and IL-12p40 production.

Another molecular lipid class was recently identified from *Morganella morganii*, a gut-resident bacterium whose prevalence has been linked to major depressive disorder (MDD) in humans. Bioassay-guided fractionation of *M. morganii* extracts revealed a group of atypical cardiolipin analogues, termed MmDEACLs, in which the bacterium utilizes the environmental micropollutant diethanolamine to replace the central glycerol backbone.[256] These hybrid lipids—molecular chimeras between endogenous phospholipid metabolites and exogenous anthropogenic compounds—activate TLR2/TLR1 receptors and induce pro-inflammatory cytokine production, particularly IL-6, mirroring the immunogenic activity and TLR selectivity of canonical cardiolipins such as SpCL-1 and MiCL-1. In contrast to the pro-inflammatory cardiolipin analogues described above, the gut symbiont *Akkermansia muciniphila* exemplifies a beneficial immunomodulatory interaction between host and microbiota.[225] This bacterium produces a diacyl phosphatidylethanolamine, 12-methyltetradecanoyl-13-methyltetradecanoyl-*sn*-glycero-3-phosphoethanolamine (a15:0-i15 : 0 PE), which engages the same TLR2/TLR1 signalling axis to trigger pro-inflammatory cytokine release under standard stimulatory conditions. However, under physiologically relevant low-dose and delayed exposure regimens, this lipid elicits the opposite outcome: a potent suppression of TNFα secretion and a resetting of the immune activation threshold.[257] These effects are consistent with a model in which repeated, low-level activation of TLR2/TLR1 signalling promotes immune tolerance and homeostasis, moderating exaggerated inflammatory responses.

Another class of microbiota-derived lipids with potent immunomodulatory properties are plasmalogens, which act as pro-inflammatory signals under specific physiologically relevant conditions. In mildly acidic environments, such as those characteristics of inflammatory niches, these vinyl ether-containing phospholipids undergo a spontaneous rearrangement to form acetal-bearing lysoglycoglycerolipids that activate TLR2-dependent signalling and induce the release of pro-inflammatory cytokines, particularly TNF-α and IL-6.

Two structurally analogous examples—EIPIsM-1 from *Eggerthella lenta* and CaPlsM from *Collinsella aerofaciens*—differ mainly in the length of their aliphatic chains yet share a common mechanism of action. In *E. lenta*, a bacterium strongly associated with inflammatory bowel disease and other autoimmune disorders, the triggered plasmalogen system provides a cell- and antigen-independent route to upregulate RORγt-dependent Th17 responses. Similarly, in *C. aerofaciens*, acidic conversion of CaPlsM yields CaLGL-1, an acetal-bearing lysoglycoglycerolipid that activates dendritic cells *via* TLR2 signalling. Although both metabolites are linked to pro-inflammatory pathways, the association of *C. aerofaciens* with favourable responses to programmed cell death protein 1/

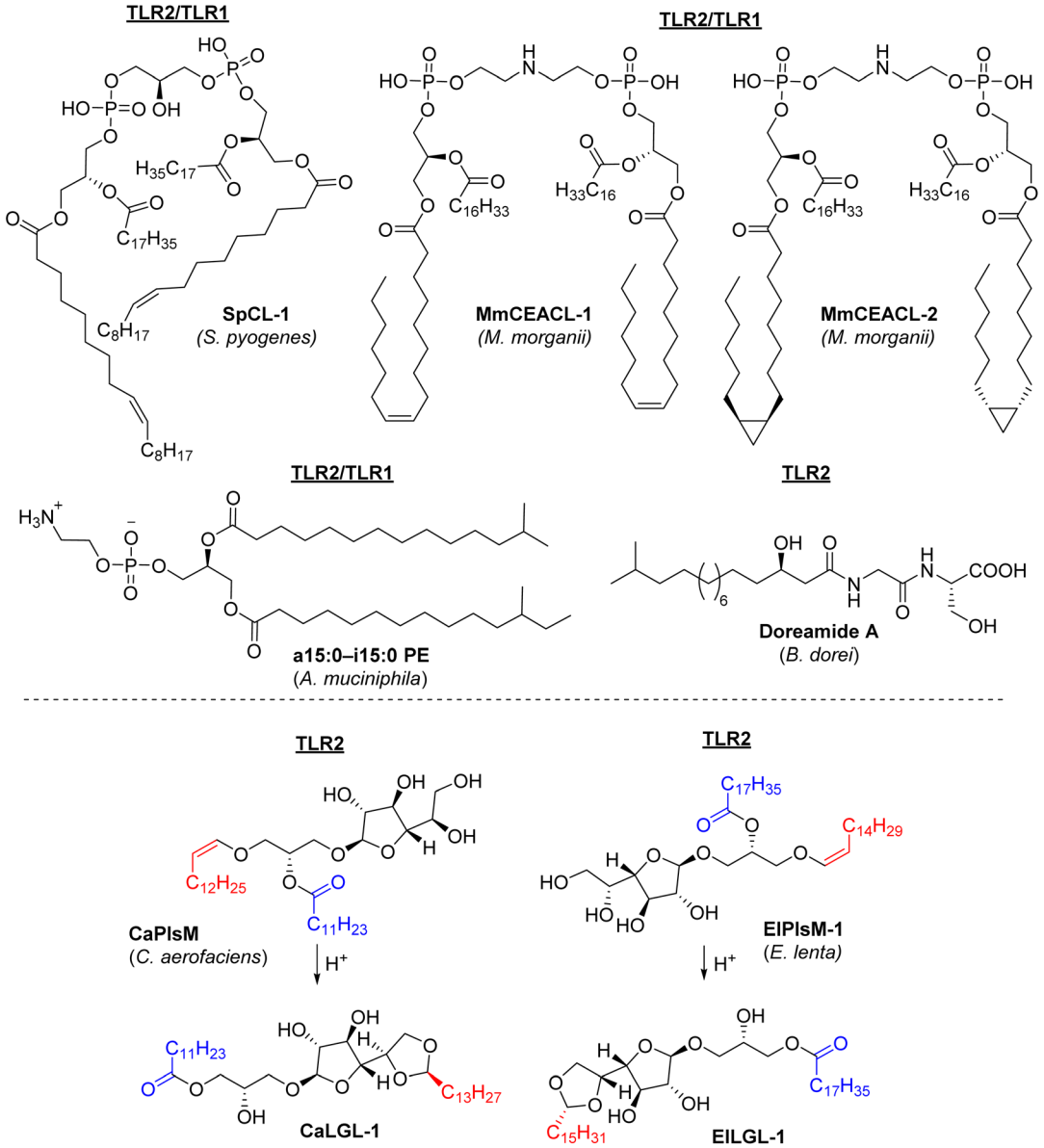

Fig. 19 Structural representations of immunogenic lipids isolated from bacterial members of the human microbiota and the corresponding human receptors that recognize them.

programmed death-ligand 1 immunotherapy suggests that such lipid-mediated immune activation can also yield context-dependent, potentially beneficial outcomes.

Additionally, recent work on the gut commensal *Bacteroides dorei* revealed that subtherapeutic exposure to tetracyclines also profoundly reshapes its secondary metabolome.[258] Using an HiTES approach, a suite of previously cryptic small molecules, namely the doreamides A-F, were uncovered, whose production is selectively induced by low-dose tetracycline antibiotics. Doreamides A–C elicit robust pro-inflammatory responses in macrophages and stimulate cathelicidin biosynthesis, a human antimicrobial peptide active against both commensal and pathogenic gut microbes. Through these activities, the doreamides modulate immune tone and likely influence microbial community structure across the gut ecosystem.

Beyond immunomodulatory and antimicrobial activities, select members of the human microbiota also produce genotoxic or proinflammatory indole-derived metabolites that directly perturb host physiology (Fig. 20) and thus are of equal importance for understanding disease occurrence and treatment.

Among these, *M. morganii*, a bacterium enriched in the gut microbiota of patients with inflammatory bowel disease (IBD) and colorectal cancer (CRC), was recently shown to synthesize a family of indole-containing small molecules termed indolimines.[259] Metabolites, such as indolimine-214, induce DNA double-strand breaks and trigger cell-cycle arrest in intestinal epithelial cells, yet their damage profiles differ from the canonical colibactin signature.[260,261] Biosynthetic studies identified a previously uncharacterized aspartate aminotransferase-

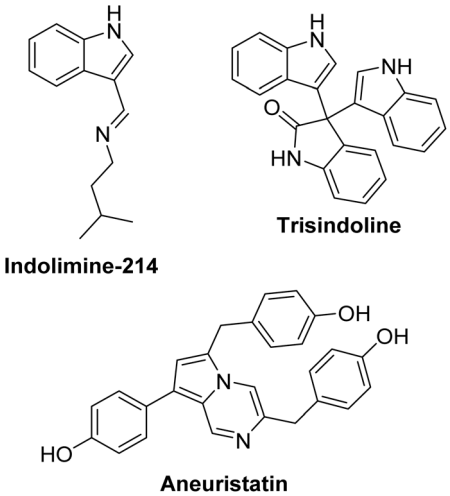

Fig. 20 Heterocyclic natural products with diverse bioactivities isolated from bacterial members of the human gut microbiota.

like enzyme (Aat) as essential for indolimine formation, and deletion of the *aat* gene abolished genotoxicity in both cell-free and cell-based assays. In gnotobiotic mouse models, indolimine-producing *M. morganii* strains increased intestinal permeability, upregulated genes associated with aberrant epithelial proliferation, and exacerbated colonic tumorigenesis.

Similarly, *Campylobacter concisus*, a gut bacterium robustly associated with Crohn's disease and ulcerative colitis, produces a structurally diverse suite of indole-containing secondary metabolites, including the compound trisindoline.[262] Especially trisindoline exhibits dual activities—selective antimicrobial effects against commensal strains and potent immunomodulatory activity mediated through aryl hydrocarbon receptor (AhR) signalling in human monocytes.[263]

Activation of this pathway induces the release of key proinflammatory cytokines such as IL-1β, IL-6, IL-8, and MCP-1, and *in vivo* imaging studies confirmed strong inflammatory responses following trisindoline administration.

Together, these findings reveal that indole-based secondary metabolites, while chemically simple, can exert profound and multifaceted effects on host immunity, inflammation, and genomic stability, providing a mechanistic link between microbial metabolism and the pathogenesis of different diseases such as IBD, Crohn's disease, and CRC.

Another striking example of microbiota-derived chemical diversity is aneuristatin, an antiangiogenic metabolite recently identified from the rare human gut bacterium *Aneurinibacillus aneurinilyticus*.[264] Erythromycin-induced activation of the *arnA* BGC triggers the production of aneuristatin, which features a distinctive pyrrolo[1,2-*a*]pyrazine scaffold. Functionally, it inhibits angiogenesis in endothelial and zebrafish models and mitigates inflammation and fibrosis *in vivo*.

5.4 Perspectives on the analysis of anti-infectives from the human microbiome

Taken together, these findings point to a clear opportunity: by probing the encoded chemical diversity of the human microbial communities, whether by studying individual producers or recreating pathways through synthetic biology, a small but growing body of wet-lab studies over recent years has highlighted the remarkable chemical and functional diversity of metabolites produced by host-associated microbiota. Many of these molecules show intriguing biological activity and entirely new chemical architectures. But despite that promise, none have yet made the move from discovery beyond pre-clinical evaluations. Another promising line of research is emerging from new insights into microbiota-derived natural products, which showed that triggering the production of secondary metabolites in commensal microbes could provide new opportunities for microbiome-based therapies and could shift the focus from simply cataloging microbes to actively harnessing their chemistry for health. The rational design of prebiotics has traditionally focused on selectively stimulating the growth of beneficial taxa such as *Bifidobacterium* and *Lactobacillus*.[265] But recent work shows that also many beneficial bacteria, including *Akkermansia muciniphila*, *Bacteroides fragilis*, and *Clostridium sporogenes*, synthesize small molecules that modulate immune response, maintain epithelial integrity, and counteract inflammation. Tailoring dietary components or small-molecule prebiotics to favour such producers could amplify the biosynthesis of protective metabolites, from immunomodulatory lipids to anti-inflammatory or neuroactive compounds, thereby improving host resilience to disease. Future efforts should combine metabolic modelling, nutrient profiling, and functional screening to design next-generation prebiotics that do not merely shape microbial composition, but steer community function toward beneficial chemical outputs. In this way, prebiotic strategies are likely to evolve from ecological manipulation toward targeted chemical modulation of the human microbiome and beyond.[266]

6 Conclusion and outlook

As demonstrated by the multitude of *in silico* metagenome studies, microbiomes constitute a vast and still largely unexplored reservoir of biosynthetic diversity making them compelling sources for anti-infective natural product discovery and for monitoring the distribution of the associated antibiotic resistance genes.[65,66] Alongside, a smaller but growing body of wet-lab studies unlocked over recent years increasing numbers of the encoded metabolites. These molecules cover a broad range of functions, from protective antibiotics and immunomodulatory lipids to genotoxins and anti-angiogenic compounds, highlighting the deep connections between microbial secondary metabolism and host physiology, immunity, development, and disease.

Despite the herein highlighted examples, microbiomes of microeukaryotes up to animals remain largely underexplored in terms of their encoded chemical space, particularly with respect to uncovering anti-infective scaffolds. As current studies are largely ecology-driven and have primarily focused on representatives of the most abundant phyla, there is a clear need for more focused and activity-driven research on culturable yet understudied microbiome members, preferentially also of key-stone

members and those that are of significance to health and disease stages of the host. In comparison to molecular and synthetic biology approaches, their ability to produce the fully matured native natural products make them still attractive targets for deeper investigation. At the same time, this approach comes with an important caveat: many microorganisms rely on highly specific environmental cues or signalling molecules found only in their native ecological niches, which explains why numerous biosynthetic pathways still remain silent under laboratory conditions, complicating efforts to link microbes to their metabolic outputs and required approaches like HiTES.[267,268]

Of similar importance to culture-based approaches are those emerging from synthetic biology, which serve as powerful complementary tools for the heterologous expression of discovered BGCs in genetically tractable hosts.[269,270] However, the large size and complex architecture of many BGCs, strain-specific codon usage, and the need for specialized substrates or cofactors remain major bottlenecks for their biotechnological exploitation and yielding often only shunt or partial structures, but seldomly the complete natural product scaffolds. These challenges highlight the need for more efficient heterologous expression systems and robust approaches to reliably capture complete BGCs, preferentially those that also show significant abundance and correlation to health and disease stages to move from correlation to causative analyses.[3]

Furthermore, most studies so far have also focused on individual strains grown in isolation or relied on heterologous expression systems, approaches that miss the rich metabolic potential that only emerges through interactions among microbes in complex communities.[271] As the bioactive repertoire of a microbiome is not simply the sum of metabolites produced by individual species, yet much of the unexplored chemical diversity, might emerge from community–level interactions in which compounds are synthesized, modified, or otherwise biotransformed across multiple taxa.[272] Moving forward and to study these effects, synthetic communities (also known as SynComs) could provide an experimentally tractable framework to dissect such interactions, enabling precise control over species composition, metabolite exchange, and environmental parameters.[273] By reconstructing simplified yet ecologically relevant consortia, SynComs might reveal emergent metabolic pathways and cryptic BGC activation that are otherwise silent in isolation, ultimately, allowing access to the predicted vast repertoire of microbiota-encoded natural products.[274] Integrating multi-omics, imaging mass spectrometry and machine learning will be key to decoding the chemical dialogue that governs interspecies interactions

Lastly, once natural products are being identified their full spectrum of bioactivities remains only partially explored, with research often only testing against a limited spectrum of test strains, and reporting primarily positive bioactivities while overlooking inactive outcomes. With the rise of advanced machine learning trained on large datasets, more systematic studies, including the reporting of inactive results, will become increasingly important to improve predictive models and fully capture bioactivity landscapes. In this context, while some molecules likely act on yet unexplored cellular targets, detailed mode-of-action studies have only rarely been conducted, limiting a full assessment of their pharmaceutical and translational potential.

In summary, despite the many advances, unraveling the encoded chemical diversity from microbiomes, turning the wealth of information and technologies for anti-infective research remains a major challenge as each approach has its own advantages and limitations. In the future, strategic combinations of genome- and pathway-guided analyses with more standardized activity-guided preselection may provide an effective approach to increase the likelihood of discovering natural products with promising activity profiles, either through exploration of native producers or *via* heterologous expression of complete biosynthetic pathways. Last but not least, more efforts in identifying the mode of actions of promising lead candidates will be essential to turn discoveries into real-world realistic prospects for translating host-associated microbiome natural products into therapeutics.

7 Conflicts of interest

There are no conflicts to declare

8 Data availability

All data in this review refers to datasets published in original articles citied within the review.

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