Insects and their antibiotic-producing bacteria

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Abstract. Many, if not all, plants and animals form mutually beneficial symbioses (mutualisms) with microbes and a subset of these mutualisms are defensive, in which the host provides food and housing in return for defence against disease. These symbioses typically involve antibiotic-producing bacteria, the best known of which are filamentous actinomycetes in the genera Streptomyces and Pseudonocardia and unicellular species in the genus Pseudomonas. Such mutualisms are likely to be widespread in nature, but they are best characterised in insects, which provide experimentally tractable models for studying symbiosis and microbiome formation because they typically host less complex microbial communities. Here, we examine the mutualisms formed between insects and antibiotic-producing bacteria using well characterised examples, including digger wasps and their endosymbiotic Streptomyces species, attine ants and their mutualist Pseudonocardia species and Pedarus beetles with their pederin-producing Pseudomonas species. We also discuss how searching such symbiotic niches can give insights into the evolution and functions of microbial specialised metabolites and provide new platforms for antibiotic discovery.
Introduction. All plants and animals form stable associations with microbes at some stage in their life cycles, and these host-associated microbial communities are commonly referred to as microbiomes. The hosts feed these microbes which in turn confer benefits to their hosts, not least the exclusion of pathogens, stimulation of the immune system and, in the case of animals, aiding the digestion of their food. Thus, mutually beneficial symbioses are widespread in nature and likely underpin the concept of healthy microbiomes [Douglas, 2019]. Within this broad definition are defensive or protective mutualisms in which one partner protects the other in return for benefits which often include food and housing. In this review we focus on antibiotic-mediated defensive mutualisms and focus on a few well characterised examples of insect hosts using antibiotics to protect themselves, their brood, or their food source against disease. This has fascinating parallels with human medicine, in which clinicians use purified and often chemically modified microbial specialised as antibiotics to either prevent or treat disease. Microbial specialised metabolites revolutionised medicine in the first half of the 20th century with the discovery of penicillin from the *Penicillium* fungus and then streptomycin from a bacterium called *Streptomyces griseus* (Lewis, 2020). The genus *Streptomyces* comprises filamentous, multicellular bacteria belonging to the phylum Actinomycetota (formerly Actinobacteria) and they and other closely related filamentous actinomycetes account for around two thirds of clinically used antibiotics (Hutchings et al., 2019). Remarkably, however, despite being studied for almost 100 years, we still have little understanding of the functions of these molecules in nature, largely because the focus has been on drug development.

The advent of whole genome sequencing at the turn of the century revitalised natural product discovery because it revealed that microbes encode many more, sometimes 10x or more, specialised metabolites than they make under standard laboratory conditions (Doroghazi and Metcalf, 2013; Nikolaidis et al., 2023). This also means that understanding specialised metabolite functions in nature and, crucially, the natural signals that activate their production,
will be crucial to the discovery of new antibiotics (van der Meij et al., 2017). We live in a microbial world, and it is self-evident that these molecules have evolved to mediate interactions in nature, between the microbes themselves and between microbes, plants and animals. Indeed, specialised metabolites can have bioactivity against bacteria, fungi, nematodes, insects and plants so without doubt some of these interactions will be used to attack other organisms or at least defend the microbes themselves against predation (van der Meij et al., 2017). Here we focus on insect hosts that use antibiotic-producing bacteria to defend themselves against disease and against predators. These examples give us insights into antibiotic use in nature and how arms races can drive evolution in mutualists and parasites.

**Pedarus beetles and *Pseudomonas*** **spp.** Pederin is a vesicant toxin of mixed polyketide/non-ribosomal peptide origin that provides a chemical defence against the arthropod predators of *Paederus* and *Paederidus* beetle eggs and larvae (Kellner and Dettner, 1996) (Figure 1). It acts by inhibiting protein and DNA synthesis, and pederin and its analogues have been investigated for their antitumor properties. Efforts to solve the chemical structure began with material isolated after grinding up 25 million beetles (Pavan and Bo, 1953) and was eventually completed through X-ray crystallographic analysis almost 20 years later which provided the absolute stereochemical configuration (Furusaki et al., 1968). Pederin is found in approximately 90% of female beetles, and only pederin-producing females can transfer the trait to their offspring. However, non-producing females can gain this trait after consuming the eggs of pederin producing females (Kellner and Dettner, 1995). This non-mendelian route of inheritance suggests a microbial origin for pederin biosynthesis and is consistent with the 16S rDNA identification of a single uncultured *Pseudomonas aeruginosa* like endosymbiont strain associated with pederin positive females (Kellner, 2002).
Two further lines of evidence provide essentially confirmatory support for the hypothesis that pederin is made by an endosymbiont rather than the beetles themselves. Firstly, antibiotic treatment of eggs from pederin producing females leads to larvae that do not produce pederin (Kellner, 2001). Secondly, a PKS (polyketide synthase)/NRPS (non-ribosomal peptide synthetase) hybrid gene cluster encoding pederin biosynthesis was cloned from total DNA isolated from Paedarus beetles. This biosynthetic gene cluster (BGC) is only found in pederin producing female beetles and their eggs, and was shown to possess genomic and biosynthetic features characteristic of bacterial systems (Piel, 2002). Strikingly, it is located within the genome of the unculturable *P. aeruginosa* strain described above where it appears to have been acquired by horizontal gene transfer and form part of what has been termed a symbiosis island (Piel, 2002; Piel et al., 2004a). This observation is intriguing as it suggests the symbiosis has origins in the horizontal acquisition of a positive-trait-providing BGC by a broad host pathogen that could infect a progenitor beetle without killing it.

Pederin like molecules include the mycalamides and onnamides and have been isolated from various species of marine sponges. The observation that such structurally similar metabolites can be identified from taxonomically distinct species provides further evidence for a microbial biosynthetic origin of pederin family metabolites. This is supported by the identification of pederin like PKS/NRPS encoding biosynthetic genes from the *Candidatus Entotheonella* endosymbionts of the sponge *Theonella swinhoei*, a source of onnamide and related theopederin metabolites (Piel et al., 2004b). The role of pederin like metabolites as taxonomically widespread ‘symbiosis factors’ is further supported by the discovery of the lichen derived molecule nosperin, and its putative BGC, from a lichen associated symbiotic *Nostoc* species of cyanobacterium (Kampa et al., 2013). More recently, pederin-like metabolites and BGCs have been reported from a range of free-living bacteria (Kačar et al.,...
Lagria beetles and Burkholderia gladioli bacteria. The herbivorous beetle Lagria villosa is an invasive pest that causes significant physical and economic damage to South American crop species. Mature Lagria beetles lay their eggs in the soil where the subsequent stages of the life cycle proceed, meaning their eggs, larvae, and pupae, are exposed to a wide range of entomopathogenic microorganisms. To gain protection against infection in this demanding environment L. villosa beetles have formed a mutualistic symbiosis with several strains of the plant pathogen Burkholderia gladioli which are only harbourred by female beetles who vertically transmit them from accessory glands onto the surface of their eggs (Stammer, 1929).

Using a combination of 16S ribosomal RNA amplicon sequencing and quantitative PCR these strains were identified as the most prevalent members of the bacterial communities present in the symbiont bearing structures of field collected adult females and their laid eggs. This and subsequent studies showed that this population comprises variable numbers of B. gladioli strains that are closely related to free living plant pathogenic relatives but includes a dominant uncultured strain B. gladioli Lv-StB which has undergone significant genome reduction and divergence (Flórez and Kaltenpoth, 2017; Waterworth et al., 2020). These strains are localised to the female reproductive glands and to specialised cuticular organs (invaginations) formed during the various life stages of L. villosa.

The role of B. gladioli strains in protecting L. villosa eggs from infection has been demonstrated by a higher frequency of fungal infection for surface sterilized eggs. Similarly, controlled exposure of eggs to spores of the fungal strain Purpureocillium lilacinum, a L. villosa egg entomopathogen (Storey et al., 1991) and known enemy of adults and larvae (Garcia and Pierozzi Jr, 1982) led to more frequent and higher level of infection amongst surface sterilized
eggs (Flórez and Kaltenpoth, 2017). Importantly, when surface sterilized eggs were reinjected
with the *B. gladioli* strain Lv-StA which was isolated from *L. villosa*, or mixtures of strains
from surface washes of native eggs, the frequency of infection by *P. lilacinum* was similarly
decreased. The authors then showed that strain Lv-StA displayed potent anti-infective *in vitro*
activity using plate assays and linked this activity and its ability to protect eggs from pathogens
to a mixture of antibacterial and antifungal molecules by using combined genome sequencing
with bioinformatics, and natural products chemistry; this included a new polyketide antibiotic
that was named lagriene (Flórez and Kaltenpoth, 2017) (Figure 1). Using similar approaches,
a hybrid polyketide/non-ribosomal peptide antifungal agent named lagriamide was identified
as a product of the dominant and unculturable strain Lv-StB and linked to the strain’s protective
effect of eggs against the pathogen *P. lilacinum* (Flórez and Kaltenpoth, 2017; Janke et al.,
2022) (Figure 1). Moreover, this strain is associated with the specialised cuticular housing
structures of *L. villosa* during all stages of the lifecycle where, through the action of the specific
antifungal molecule lagriamide, it plays a key role in defence against pathogens (Janke et al.,
2022).

The BGC encoding production of lagriamide in strain Lv-StB was likely acquired via
horizontal gene transfer (HGT) (Waterworth et al., 2020), and this metabolite is closely related
to other so called bistramide metabolites isolated from marine ascidians, and which are
believed to derive from their bacterial symbionts (Gouiffès et al., 1988). The structural
similarity of these metabolites is consistent with a common biosynthetic origin and
dissemination of the BGC through HGT, possibly indicating a role as effective ‘symbiosis
factors’ as highlighted above for pederin like molecules (Piel et al., 2004a). Thus, *B. gladioli*
Lv-StB and its product lagriamide appear to act as the main protective symbiont of *L. villosa*
which is housed in specialised structures throughout the beetle lifecycle and which the authors
suggest may provide resources for its survival and propagation (Janke et al., 2022). The presence of additional *B. gladioli* species represents a dynamic situation, and their close relationship to pathogenic *B. gladioli* strains was demonstrated for the isolated strain Lv-StA which can infect soybean plants and act pathogenically after both direct inoculation and exposure to beetles carrying the strain. This suggests bidirectional transfer is a common event with the free-living strains able to take advantage of the host environment. This loose and dynamic arrangement provides an association with multiple protective *B. gladioli* strains, and as shown for at least the example of strain Lv-StA, a cocktail of anti-infective metabolites. This adaptive capability may enable the inhibition of a wide range of pathogens and additionally provide protection against the selection for resistant organisms and mirrors the use of multidrug therapy for this same reason in human medicine.

**Beewolf solitary digger wasps (Philanthus spp.) and Streptomyces.** These digger wasps are unusual because they form an endosymbiosis with *Streptomyces philanthi* which is undergoing genome reduction (Nechitaylo et al., 2021). When nesting, the female beewolves dig underground burrows in the soil, and place paralysed honeybees in the burrows as food for their larvae, and they protect their cocooned larvae against bacterial and fungal infections using the *Streptomyces* bacteria that grow inside the female antennal glands. The female wasps secrete large amounts of a white substance out of their antennal glands into the brood cell, and these secretions are largely made up of *Streptomyces philanthi* bacteria (Kaltenpoth et al., 2006; Seipke et al., 2012). The larvae take up the symbiotic *Streptomyces* bacteria from the mother’s secretion droplets and spin them into their cocoons where the bacteria produce antibacterial and antifungal metabolites that protect the developing larvae against infection; the presence of these bacteria significantly increase survival of larva in the presence of pathogenic microorganisms (Kaltenpoth et al., 2005).
Chemical analysis of the cocoons identified nine different antibiotics comprising streptochlorin and a complex of eight different congeners of piericidin, and although the total quantities of metabolites varied between cocoons, the distribution of components was found to be relatively constant (Kroiss et al., 2010) (Figure 2). When the Streptomyces spp. was removed from the beewolf brood cells none of these metabolites could be detected in the resulting cocoon. Subsequently, streptochlorin and the piericidins $A_1$ and $B_1$, the three major components of the antibiotic complex, were directly visualized on the cocoons using imaging mass spectrometry. The susceptibility of a range of pathogenic microbes was shown to be variable when tested against several of the individual antibiotic components, whereas the growth of all these strains was strongly inhibited when the complete mixture was present. These data support both a complementary action of the various substances and the idea that the digger wasps are using multidrug therapy to protect their larvae, and this could also explain why the pathogens that challenge these larvae do not evolve resistance to Streptomyces philanthi antibiotics (Koehler et al., 2013).

**Leafcutter ants of the tribe Attini and Pseudonocardia spp.** Attine ants practise one of the earliest known forms of agriculture, feeding plant material to a symbiotic fungus that provides them with the sole food source for their larvae and queen (Batey et al., 2020). They are endemic to South and Central America and the Southern USA and the most highly derived attines are leafcutter ants in the genus Acromyrmex and Atta (Schultz and Brady, 2008). Remarkably, they have evolved a tripartite mutualism with their fungal cultivar and with actinomycete bacteria in the genus Pseudonocardia which defends the ants against fungal parasites in the genus Escovopsis (Currie, 2001). In Acromyrmex echinatior ants collected in Gamboa, Panama, the Pseudonocardia symbiont belongs to one of two species clades and the ants vertically transmit a single strain of this symbiont along with their food fungus (Holmes et al., 2016). The ants
house their fungal cultivar, *Leucoagaricus gongylophorus*, in garden chambers in their underground nests where they feed it cut leaves. Their larvae feed on specialised hyphal structures called gongylidia that are rich in fats and sugars and provide the sole food source for the ant colony (Currie, 2001). They house their *Pseudonocardia* symbiont on the external face of their cuticles and feed the bacteria through specialised glands and, in return, this symbiont produces antibacterials which prevent most other bacteria from colonising (Currie et al., 2006; Worsley et al., 2021) and antifungal metabolites that the ants use to defend their cultivar against *Escovopsis weberi* (Goldstein and Klassen, 2020). The food provided to the ants has not been identified but the most highly upregulated genes in *Pseudonocardia* bacteria living on the ants encode enzymes involved in the degradation of waxy fatty acids (Worsley et al 2021). In *Acromyrmex* ant colonies, the *Pseudonocardia* symbiont strains make polyene antifungals that are closely related to nystatin A (Barke et al., 2010; Holmes et al., 2016) (Figure 3). Another nystatin-like molecule called selvamicin has also been discovered from a *Pseudonocardia* symbiont associated with *Apterostigma* attine ants (Figure 3) (Van Arnam et al., 2016).

*Acromyrmex* ants have also been shown to house *Streptomyces* species which appear to be resistant to the antibacterials made by *Pseudonocardia* (Haeder et al., 2009; Kost et al., 2007; Seipke et al., 2011). These *Streptomyces* species are also fed by the ants (Worsley et al., 2021), which provide public resources to all their cuticular bacteria, and they also make antifungal metabolites, but it is not clear if they are mutualists or transient passengers on the ants (Seipke et al., 2011). A second major class of antifungals produced by attine derived *Pseudonocardia* mutualists are the cyclic piperazine containing non-ribosomal peptides called the dentigerumycins (Oh et al., 2009) (Figure 3). The first example, dentigerumycin A, was isolated from the lower attine *Apterostigma dentigerum* and showed remarkable selectivity for the *Escovopsis* pathogen over the *Leucoagaricus* cultivar. Remarkably the *Escovopsis* parasites fight back, producing an insect feeding deterrent called emodin, insect neurotoxins called
shearines which inhibit the ant behaviours and are ultimately lethal, and melinacidins, which are antibiotics that kill Gram-positive bacteria, including *Pseudonocardia* and *Streptomyces* species (Dhodary et al., 2018; Gotting et al., 2022; Heine et al., 2018) (Figure 4).

Protection of pollinators and their plants by *Streptomyces* species. Suppressive soils are defined as soils in which a pathogen is unable to establish or persist; establishes but causes little damage; or establishes leading to disease, but subsides over time to become less of a problem (Gómez Expósito et al., 2017). This protective effect is driven by the soil microbiome and can be general, where the gross microbiome provides low levels of protection, or specific, where a single or small group of beneficial microbes provide strong protection, often to a specific plant or crop type. A key characteristic of specific suppressiveness is that it can be transferred to non-suppressive, or conducive, soils through their mixing. Probably the best studied example of the latter is wheat Take-all decline, which develops following an outbreak of the root pathogenic fungus *Gaeumannmyces tritici*. This effect is believed, in part, to arise from phenolic metabolites with antibiotic activity called phloroglucinols produced by beneficial *Pseudomonas* species which build up in the soil following continuous wheat or barley monoculture (Kwak and Weller, 2013).

Another highly informative example that provides linkage between a bacterial species and a specific suppressive soil effect has been reported for a *Streptomyces* spp. which protects field planted strawberry plants from necrotrophic *Fusarium oxysporum* f. sp. *fragariae* wilt disease. The authors studied a managed strawberry ecosystem in Jinju South Korea, where they identified a mutualistic plant-microbe partnership that forms part of a tripartite symbiosis that involves an insect pollinator (Kim et al., 2019). Necrotrophic grey mould disease caused by the phytopathogen *Botrytis cinerea* is endemic amongst greenhouse-grown crops such as...
strawberries and is spread easily through the airborne transfer of spores. Through longitudinal
analysis (16S rDNA amplicon sequencing) of the flower and pollen microbiota across the
growing season, a shift from a high- to low-diversity microbiota was shown to correlate with a
significant increase in the rate of *B. cinerea* disease incidence. This shift was coincident with
a decline in *Streptomyces* strains, most notably strains indistinguishable from *Streptomyces
globisporus*. Following isolation and screening for antifungal activity, 66 isolates (44 from
flowers and 22 from pollen) were identified as beneficial, with 16 strains assigned as *S.
globisporus*, *S. griseus* or *Streptomyces badius* species using multigene phylogeny analysis.
All of these species have been categorised as belonging to the *S. griseus* group (Rong and
Huang, 2010), and two (SP6C4 and SF6B6), which were collected from different sources and
at different times, showed potent antifungal activity against *B. cinerea* and colonization activity
on flowers. Surprisingly, genome sequencing of these two isolates showed they were
indistinguishable from the S4-7 strain identified from the suppressive soil study above and thus
were re-classified as *S. globisporus* sp. S4-7, SP6C4 and SF6B6. These observations led the
authors to hypothesise that *S. globisporus* strains in the rhizosphere can colonize plants and
become endophytic, before migrating through the plant vasculature and establishing on flowers
and in pollen where they can transfer to pollinators. Using tagged versions of strain SP6C4,
translocation from both the rhizosphere and flowers into stem vascular bundles was validated,
as was plant to plant transfer by honeybee pollinators; the bacteria also successfully colonized
the honeybee gut. Subsequently, using leaf spraying experiments, it was demonstrated that
SP6C4 can significantly reduce the incidence of grey mould disease (Kim et al., 2019). In the
final part of this study the authors probed the possibility that *S. globisporus* isolates can protect
pollinators by feeding caged honeybee populations with pollen containing either of the
entomopathogens *Paenibacillus larvae* or *Serratia marcesens*. While the controls fed pollen
containing no bacteria or strain SP6C4 for 5 days showed identical 28% mortality, honeybees
fed pollen containing either *P. larvae* or *S. marcesens* showed 73% or 88% mortality respectively. When pollen was fed containing each entomopathogen in combination with strain SP6C4 then the mortality was decreased by approximately 50%. Thus, in this tripartite system the *Streptomyces* species is vectored by the pollinator and provides protection against both pathogenic fungi and bacteria. Single *Streptomyces* species are known to encode the production of numerous antimicrobial molecules, the majority of which are not expressed under laboratory conditions, but which likely provide some ecological benefit. This work was all published in a single study and so it will be important to explore this system further and to understand the regulation and identify of the metabolites produced by the *S. globisporus* strain(s).

**Antibiotic discovery from under explored niches.** Many of the antibiotics identified from defensive mutualisms belong to known classes but may still have utility, e.g., the multiply glycosylated nystatins made by the *Pseudonocardia* symbionts of *Acromyrmex* ants which are significantly more soluble than the clinically used nystatin A1 while retaining good activity against pathogenic fungi (Barke et al., 2010; Won et al., 2017). Moreover, strains isolated from other fungus farming ants can yield new structural classes of antibiotic, an intriguing example of which is the isolation of the formicamycins from the nest of the Kenyan plant ant *Tetraponera penzigi* (Qin et al., 2017). These ants protect Acacia trees against herbivores (Palmer et al., 2021) and the ants live inside specialised structures on the plant called domatia where they grow a fungus as food (Baker et al., 2017). Several new species were isolated from this niche and shown to make novel antibiotics, including a *Saccharopolyspora* strain making a lantipeptide antibiotic (Vikeli et al., 2020). Another new species from this niche, called *Streptomyces formicae* KY5, makes formicamycins which represent a new structural class of antibiotic (Figure 5). Remarkably this strain has acquired four genes which expand a known pathway for the biosynthesis of fasamycins, which was first cloned from environmental DNA...
In *S. formicae* the fasamycins are biosynthetic precursors of formicamycins but both sets of metabolites have potent activity against MRSA and a high barrier to the selection of resistant strains (Feng et al., 2012; Qin et al., 2020, 2017).

Another example is the potent antibiotic darobactin, which is produced by a nematode symbiont in the genus *Photorhabdus* and selectively kills Gram-negative bacteria and (Imai et al., 2019) (Figure 5). These bacteria colonise the guts of entomopathogenic nematodes which infect susceptible insects, and the bacteria are then released into the insect haemolymph where they kill the insects. They are then consumed by the nematodes and recolonise the nematode guts to start the life cycle over again (Clarke, 2020). Darobactin is a ribosomally synthesized and post-translationally modified peptide (RiPP) which targets BamA, which is surface exposed on the outer face of the outer membrane. BamA is the central component of the essential BamACDE complex which inserts proteins into the outer membrane of *E. coli*. Crucially, spontaneously resistant mutants which mapped to *bamA* were avirulent in mice suggesting resistance to darobactin also blocks the ability of *E. coli* to cause disease. Intriguingly these are the first BamA targeting metabolites to be identified but given this essential protein is surface exposed in *E. coli* and its close relatives, the authors suggest it is likely that more BamA targeting molecules are waiting to be discovered (Imai et al., 2019).

A third and final example is provided by attinimicin, an antibacterial non-ribosomal peptide which was identified following a systematic study of *Pseudonocardia* spp. isolated from attine ants collected across four geographical regions of Brazil (Fukuda et al., 2021) (Figure 5). Intriguingly, although attinimicin resembles siderophore structures, and binds ferric iron with moderate affinity, it was shown that iron bound attinimicin had no inhibitory activity towards pathogenic *Escovopsis* spp. but showed some activity when depleted of iron and was further
shown to provide protection in a mouse model of *Candida albicans* infection. In contrast, it showed no activity towards the *Leucoagaricus* cultivar species in a similar fashion described for the dentigerumycins above.

**Concluding remarks.** The examples presented here demonstrate that plants and animals have been using antibiotic-producing bacteria to defend themselves for millions of years and do not appear to have problems with antibiotic resistant pathogens. This does not compare favourably with humans, who have been using purified metabolites as antibiotics for almost 100 years, and already have multidrug resistant pathogens that cannot be treated effectively (Lewis, 2020). Insects use antibiotics differently; they form mutually beneficial symbioses in which they exchange food and housing for protection by bacteria that make multiple antibiotics and this likely slows the evolution of resistance. Typically, these insects vertically transmit their mutualist bacteria from mother to offspring, but insects can also acquire their bacteria anew from the environment in each generation. A great example of this is the squash bug *Anasa tristis* which needs bacterial symbionts in the genus *Caballeronia* to survive. These insects have acquired specialised acquisition behaviours that enable their nymphs to find and select the bacteria they want from adult faeces (Villa et al., 2023). This is another example of how insects provide simple but effective models for understanding symbiont transmission and maintenance and more generally for studying how microbiomes are assembled (Douglas, 2019). Although relatively few examples have been studied in any detail, such mutualisms are likely to be widespread in nature and understanding their functions, and the communication and chemical signalling between partners, may also help us to unlock some of the thousands of cryptic specialised metabolites encoded in microbial genomes that are not made under laboratory conditions (Doroghazi and Metcalf, 2013).

Exploring such competitive niches, combined with genome mining and editing tools, is
highly likely to provide a new source of functionally valuable metabolites that could replenish the pipeline for antibiotic development. Indeed, it has been reported that *Streptomyces* species isolated from insect microbiomes are a rich source of antimicrobials (Chevrette et al., 2019). Furthermore, the microbes themselves could be used as biologicals to protect crop plants against pests and pathogens. Also, while insect mutualisms are important for insect health, they also have downstream effects on plant reproduction and protection, all of which are important to human survival. Climate change, and the concomitant rising temperatures, will affect not only insect fertility and reproduction but will also affect their ability to maintain these mutualisms and the pathogens that make such mutualisms attractive to their hosts (Vidal et al., 2021) so this can be expected to have negative downstream effects on crops. Thus, insect mutualisms not only provide a good model for understanding symbiosis (Douglas, 2019) but also have a wider importance in food security and human health and are thus worthy of future study.

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Figure 1. Compounds isolated from the bacterial symbionts of Paederus and Lagria villosa beetles
Figure 2. Molecules made by the Streptomyces endosymbiont housed inside the digger wasp antennal glands. The major metabolites are shown on the left and minor piercidin congers on the right hand side of the digger wasp image.
Figure 3. Molecules made by vertically transmitted Pseudonocardia and Streptomyces strains associated with attine ants
Figure 4. Molecules made by the attine ant fungal pathogen Escovopsis weberi to kill attine ants and their beneficial bacteria
Figure 5. New antibiotics discovered from bacteria living in symbiotic niches.

*Streptomyces formicae*  
*Photorhabdus*  
*Pseudonocardia*