Chemical Ecology of Nematodes

Ricardo A. R. Machado*§ and Stephan H. von Reuss*§

Abstract: Nematodes represent the most abundant group of metazoans on Earth. They utilize diverse chemicals to interact with conspecific organisms and are also impacted by compounds produced by other interacting heterospecific organisms. In the first part of this review we discuss how nematode-derived glycolipids modulate their behavior and development, as well as the interactions with other organisms. Furthermore, we provide a short overview about other secondary metabolites produced by nematodes that affect different life traits of free-living nematodes. In the second part of this review we discuss how different bacteria-, fungi-, nematode-, and plant-derived chemicals such as volatile organic compounds, root exudates, and plant defenses regulate the interactions between entomopathogenic nematodes, their symbiotic bacteria, insect prey, predators, and plants.

Keywords: Chemical ecology · Chemical signaling · Nematodes

Ricardo A. R. Machado studied Agronomic Engineering at Universidad Nacional de Colombia (Colombia) and Microbiology at the University of Hamburg (Germany). He then did his PhD at the Max Planck Institute for Chemical Ecology (Germany). In 2015, he moved to the University of Bern (Switzerland). In 2020, he established his research group in the University of Neuchâtel (Switzerland) supported by an Ambizione Fellowship. His research interest relays on the chemical and molecular ecology of terrestrial ecosystems and on the taxonomic and phylogenetic relationships of entomopathogenic nematodes and their symbiotic bacteria.

Stephan H. von Reuss (born 1975 in Germany) obtained his PhD in organic chemistry from the University of Hamburg in 2009. After postdoctoral studies at Cornell University (Ithaca, USA) he establish his research group in 2012 at the Max Planck Institute for Chemical Ecology in Jena. In 2016 he was appointed to full professor at the Institute of Chemistry of the University of Neuchâtel, where he leads the Laboratory for Bioanalytical Chemistry and serves as director of the Neuchâtel Platform of Analytical Chemistry. His major research interests include the ecology and evolution of secondary metabolism and chemical signaling in nematodes.

1. Introduction

Nematodes are non-segmented roundworms, typically 5–100 µm thick and 0.1–2.5 mm long, although some parasitic species can reach up to 1 m in length.[1] They possess digestive, nervous, excretory, and reproductive systems, but lack a discrete circulatory or respiratory system.[1] Nematodes are the most abundant group of metazoans on Earth. Up to 2019, there were almost 30,000 nematode species described[2] and it is estimated that more than 1 million nematode species could possibly exist.[2,3] Nematodes have adapted to nearly every terrestrial and aquatic ecosystem. They are found from the tropics to the polar regions as well as deep below ground and on top of the highest mountains.[4] Nematodes are classified using different criteria. For instance, in terms of feeding guilds, they are classified as detritivores, bacterivores, fungivores, herbivores, omnivores and predators.[5] Depending on the potential requirement for a host to complete their life cycle, they are also classified as free-living or parasitic. Free-living nematodes typically feed on detritus, bacteria, fungi, algae, or other nematodes, whereas parasitic nematodes infect plants and other animals such as insects or mammals, including humans.[6]

Some nematode species have attracted considerable attention because they serve as essential model organisms in medicine, biology, and other domains including chemical ecology.[7] In this review on nematode chemical ecology, we focus on free-living bacterivorous nematodes such as the model organism Caenorhabditis elegans and related species, as well as entomopathogenic nematodes (and their associated symbiotic bacteria) to describe how chemical signals produced by the nematodes impact conspecific and heterospecific organisms, and how chemicals produced by heterospecific organisms impact different life traits of nematodes.

2. Chemical Ecology of Free-living Nematodes

While chemical signaling in free-living nematodes has been known since the 1960s,[8] molecular structure assignment of the underlying effectors has only commenced during the last decade. Ongoing research has revealed an unexpected diversity of modular structures that combine building blocks from diverse primary metabolic pathways. Hundreds of nematode-derived compounds have been identified, but biological functions have only been elucidated in a limited number of cases.

2.1 Ascaroside Signaling in Nematodes

Chemical communication in nematodes is modulated by ascarosides, glycolipids of the 3,6-dideoxy sugar l-ascarylose linked to homologous fatty acid derived aglycones (Fig. 1). Ascarosides are widely conserved in nematodes[9] and represent key regulators in nematode chemical ecology. More than 300 different ascaroside structures have been identified. The ascaroside profile of the model organism Caenorhabditis elegans undoubtedly represents the most well studied system,[10] along with a collection of related Caenorhabditis species from the Elegans group[11] and the

*Correspondence: Prof. S. von Reuss*, E-mail: stephan.vonreuss@unine.ch; Dr. R. A. R. Machado*, E-mail: ricardo.machado@unine.ch

*Institute of Biology, University of Neuchâtel, CH-2000 Neuchâtel; *Institute of Chemistry, University of Neuchâtel, CH-2000 Neuchâtel.

These authors contributed equally to this review.
satellite model organism *Pristionchus pacificus*,[12] whereas other families are much less understood. Whereas simple ascarosides, carrying saturated or α,β-unsaturated homologous sidechains ranging from 3 to 13 carbons, are most highly conserved in nematodes,[9] there also exists an as yet largely uncharacterized plethora of species-specific components. This high degree of ascaroside diversity originates from species-specific modifications (Fig. 2) that include a) hydroxylation of aglycones;[11b,d,13] b) epimerization of the L-ascarylose moiety to furnish L-paratosides[12a] or L-caenorhabdosides;[11d] c) homo and hetero-dimerization of conserved monomeric building blocks[11l,12a,d] d) as well as the modular assembly of additional building blocks derived from diverse primary metabolic pathways.[10c,i,m,18,25] Systematic analysis of 32 culturable *Pristionchus* species suggested convergent evolution of ascaroside biosynthesis.[12d] Furthermore, various very long chain 2-hydroxyalkyl ascarosides from the eggs of parasitic *Ascaris lumbricoides* have been linked to their resistance.[15] Similar compounds have also been identified from *C. elegans*.[10b,16]

Analytical techniques capable of detecting known as well as yet unidentified ascarosides and to facilitate their structure assignment have been developed over the last decade based on the differential analysis of dqf-COSY spectra,[10b] ESI-(–)-MS/MS precursor ion screening,[10f,h] screening for characteristic marker ions in GC-EI-MS chromatograms of TMS-derivatized nematode metabolomes,[11b,16b] comparative metabolomics,[10b,k,12e,17] MS/MS molecular networks,[10b,17a,d] and microcrystal electron diffraction.[10e] However, even for bacterivorous nematodes like *C. elegans* that can be easily mass-cultivated, the fact that most ascarosides are only present in very small quantities as part of extremely complex mixtures, implies the requirement of total synthesis in order to confirm structure assignments and to obtain pure materials for their functional characterization.

### 2.2 Ascarosides Modulate Nematode Behavior and Development

Nematode-derived ascarosides elicit responses in conspecific and heterospecific nematodes as well as a diversity of other organisms, indicating that they represent key regulators in nematode chemical ecology. In *C. elegans* ascarosides control nematode behavior and development. Synergistic blends of simple ascarosides, especially asc-C6-MK (6, n = 2, ascr#2), asc-ΔC9 (2, n = 4, ascr#3), and asc-οC3 (ascr#5) control dauer development.[10b,14,19] Dauer activity of ascarosides is highly structure dependent.[10a,19] Comparative analysis of food-dependent dauer development in various *C. elegans* strains demonstrated diverse responses, thus suggesting potentially manipulative ascaroside signaling.[20] Asc-C6-MK (6, n = 2) and asc-ΔC9 (2, n = 4) regulate *C. elegans* lifespan and stress resistance.[21] Predominantly male produced asc-Ç9 (1, n = 4, asc#10) primes the *C. elegans* female reproductive system and limits the effects of heat stress,[22] increases duration of *C. elegans* reproduction,[23] and improves the quality of the oogenic germline.[24] In addition, asc-ΔC9 affects nematode behavior, by modulating attraction,[10k] aggregation,[10] as well as avoidance and repulsion.[10a,k,14,25]

**Fig. 1.** Ascaroside biosynthesis via peroxisomal β-oxidation.

**Fig. 2.** Selection of species-specific ascarosides.
Similar ascarioside responses on nematode behavior and development have been characterized in other species. Males of gonochoristic Caenorhabditis inopinata, the sister species of C. elegans, are attracted to simple ascariosides.\textsuperscript{[14]} Males of the gonochoristic Caenorhabditis remanei and Caenorhabditis nigoni are exclusively retained by their conspecific ascarioside dimers.\textsuperscript{[11]} Males of C. remanei are retained by female-produced fatty acid ascariosides.\textsuperscript{[11]} Modular indole ascariosides act as attractants in various Caenorhabditis species.\textsuperscript{[11]} C. elegans shows the strongest retention to the conspecific asc-ΔC9-PABA (7, ascr#8) in comparison to various related Caenorhabditis species.\textsuperscript{[26]}

Dauer development in hermaphroditic Caenorhabditis briggsae is regulated by asc-C6-MK (6, n = 2).\textsuperscript{[18]} Two sex-specific mating pheromones asc-C7 (1, n = 2, ascr#1) and asc-3,8-OH-C11 (8, dhas#1) attract both males and females in gonochoristic Panagrellus redivivus.\textsuperscript{[13]} Males of the three-<ref>gendered Asaena rhodensis (SB347) prefer mating with females over hermaphrodites, due to female-specific production of asc-C5 (1, n = 0, ascr#9) and asc-C7 (1, n = 2).\textsuperscript{[15]} Asc-C5 (1, n = 0) influences reproductive plasticity in pine wilt nematode Bursaphelenchus xylophilus.\textsuperscript{[28]} Entomopathogenic nematodes (EPNs) such as Heterorhabditis spp. and Steinernema spp. produce and respond to ascarioside signals,\textsuperscript{[29]} which affect their recovery, yield, and dispersal.\textsuperscript{[30]} Asc-C5 (1, n = 2) along with other yet unidentified components regulates EPN dispersal.\textsuperscript{[31]} The ethanolamide asc-C11-EA (9) induces formation of infective juveniles in Heterorhabditis bacteriophora.\textsuperscript{[32]} In Pristionchus pacificus dauer development and mouth form dimorphism that enable a predatory lifestyle are regulated by highly species-specific modular ascariosides dasc#1 (10) and npar#1 (11).\textsuperscript{[1]l,2ace} Natural variation in dauer pheromone production and sensing suggests a role in intraspecific competition.\textsuperscript{[12bc,33]}

Furthermore, the dominating ascarioside of plant parasitic Meloidogyne spp., asc-C11 (1, n = 6, ascr#18), induces plant defense mechanisms\textsuperscript{[34]} and enhances pathogen resistance.\textsuperscript{[35]} Several basic ascariosides induce trap formation in nematophagous Arthrobotrys fungi.\textsuperscript{[36]} Nematode-derived ascarioside asc-C5 (1, n = 0) promotes the prevalence of ophistomatoiid fungi associated with the plant-parasitic B. xylophilus,\textsuperscript{[37]} triggers increased reproduction in invasive strains\textsuperscript{[28]} and sympatric sibling species.\textsuperscript{[38]} Furthermore, asc-C5 (1, n = 0) coordinates the nematode’s dispersal with the metamorphosis of its main vector beetle Monochamus alternatus,\textsuperscript{[39]} whereas asc-C9 (1, n = 4) regulates the insect’s cold acclimation.\textsuperscript{[40]}

Ascariosides released by animal parasitic nematodes modulate host immune responses. Acute treatment with ascariosides improves hepatic inflammation in aged mice.\textsuperscript{[41]} Ascarioside release by parasitic species, especially asc-ΔC7 (2, n = 2, ascr#7) attenuate mammalian type 2 inflammatory responses.\textsuperscript{[42]} The Na-ASP-2 protein secreted by parasitic hookworms, Necator americanus binds asc-ΔC9 (2, n = 4) and has been hypothesized to function in immune evasion.\textsuperscript{[43]}

2.3 Biosynthesis of Ascariosides

Biosynthesis of the homologous ascarioside series depends on the peroxisomal β-oxidation cycle involved in fatty acid catabolism (Fig. 1). Peroxisomal β-oxidation mutants lack the short chain signaling molecules and accumulate long-chain biosynthetic precursors.\textsuperscript{[10k,16b,44]} Functions of acyl-CoA oxidas (acox),\textsuperscript{[10k,16b,44]} enol-CoA hydratase (maoc-1),\textsuperscript{[10k,16b,44]} 3-hydroxyacyl-CoA dehydragenase (dhls-28),\textsuperscript{[10k,16b,44]} and 3- ketoacyl-CoA thiolase (daf-22)\textsuperscript{[10kb,ka,16b,45]} have been characterized. As expected for a canonical primary metabolic pathway, various orthologs have been identified in other nematodes. Chb-daf-22 from C. briggsae is required for production of short-chain ascariosides.\textsuperscript{[11g]} Bx-daf-22 contributes to mate attraction in gonochoristic B. xylophilus.\textsuperscript{[46]} Two Ppa-daf-22 paralogs from Pristionchus pacificus have been linked to dauer development.\textsuperscript{[47]} Hc-acox-1,\textsuperscript{[48]} Hc-maoc-1,\textsuperscript{[49]}

Hc-dhs-28,\textsuperscript{[50]} and Hc-daf-22\textsuperscript{[51]} orthologs have been characterized in Haemonchus contortus and linked to the regulation of dauer.\textsuperscript{[51b]}

In contrast to the chain shortening of the aglycone during peroxisomal β-oxidation, the biosynthesis of the key 3,6-dideoxy sugar, the l-ascarylose unit, has remained enigmatic. Ascarioside production in axenic media unambiguously established its nematode origin\textsuperscript{[45]} and several putative biosynthetic genes have been assigned, which, however, have been demonstrated to be linked to l-hamnose biosynthesis.\textsuperscript{[32]}

Combination of comparative metabolomics and genome-wide association mapping (GWAS) with multiple Pristionchus pacificus strains revealed a carboxyltransferase (Ppa-aar-1) involved in biogenesis of modular ascariosides like ubas#1\textsuperscript{[12c]}. Subsequently, an orthologous family of carboxyltransferases (CEST) enzymes specialized in lysosome related organelles (LROs) have been characterized in C. elegans and shown to be involved in the biogenesis of various modular ascariosides.\textsuperscript{[17a,b,23]}

Ascarioside signals present in the nematode’s environment are taken up and further metabolized by β-oxidation and attachment of additional building blocks.\textsuperscript{[10j,q]} Metalomembrane chain ascariosides has been explored by feeding [1C]-labeled ascariosides\textsuperscript{[17b]} or alkyne-labelled derivatives for click-chemistry-based enrichment of the corresponding metabolites.\textsuperscript{[44]} Furthermore, nematode-derived ascariosides are also edited by plants,\textsuperscript{[55]} fungi, bacteria, and mammals.\textsuperscript{[17b]} Activated biosynthetic acyl-S-CoA intermediates have been tagged by reaction with 4’-NH2 OH.\textsuperscript{[56]}

Ascarioside biosynthesis is highly species-specific and depends on the nematode’s sex\textsuperscript{[10g,11e,13,27]} and developmental stage.\textsuperscript{[14a,b,57]} as well as the nutritional state\textsuperscript{[10a,b,k,21l,57]} and the bacterial food source\textsuperscript{[s]116} of the producing organism. Ascarioside production is upregulated by temperature stress via the heat-shock transcription factor hsf-1.\textsuperscript{[58]}

Ascarioside production in entomopathogenic Steinernema spp. is largely independent of symbiotic versus non-symbiotic bacteria.\textsuperscript{[59]} In contrast, indole ascariosides in bacterivorous C. elegans depend on the availability of l-tryptophan within the bacterial diet and thereby link nematode aggregation behavior to nutritional status.\textsuperscript{[10a]}. Similarly, biogenesis of a highly species-specific female-produced male attractant in C. remanei depends on the developmental stage-dependent lipid cyclopropanation in the bacterial food source and thereby links nematode behavior to the bacterial growth phase.\textsuperscript{[11d]}

2.4 Other Signaling Molecules from Nematodes

Whereas our current understanding of nematode effectors suggests an outstanding importance of ascarioside signaling, this impression might simply reflect our previous emphasis on this group of metabolites. Ongoing research demonstrated that nematodes produce a diversity of additional secondary metabolites, many of which are capable of modulating their development and behavior (Fig. 3). Male-produced (2E,4Z,7Z)-N-decatrienyl-glutamine (nacq#1)\textsuperscript{[13]} promotes dauer recovery in hermaphrodites and accelerates larval development.\textsuperscript{[60]} Indole-N-glucoside (iglu#1)\textsuperscript{[14]} represents a detoxification product of E. coli-derived indole.\textsuperscript{[61]} Anthranilic acid glucoside (ang#1#15) is accumulated in LROs and released upon nematode death.\textsuperscript{[62]} Based on these and other glucosides a diverse library of modular glucosides (mogl)\textsuperscript{[16]} is accumulated in the C. elegans endometabolome, especially upon starvation.\textsuperscript{[17a,c]} The nemamides\textsuperscript{[17]} represent the first (and only) mixed PKS-NRPS metabolites produced by multicellular organisms and promote survival during starvation-induced larval arrest.\textsuperscript{[63]} Sulfolipids\textsuperscript{[18]} are released upon rupture of nematodes and serve as alarm pheromones.\textsuperscript{[64]} The lipophilic polyunsaturated wax ester nematol\textsuperscript{[19]} facilitates nematode aggregation to form ‘towers’ involved in phoresy.\textsuperscript{[65]} Homologous maradolipids\textsuperscript{[20]} with a 6,6’-diacyltrehalose core structure are exclusively produced
in the dauer stage but their function remains unknown. Several homologous N-acyl phosphoethanolamine (21) have been identified in C. elegans. [74,76,77,79] Taken together, these results suggest that ascarosides represent only a small fraction of small molecule signals involved in nematode chemical ecology.

3. Chemical Ecology of Entomopathogenic Nematodes and their Symbiotic Bacteria

Entomopathogenic nematodes (EPNs) are soil-dwelling organisms that parasitize and kill small arthropods, including insects, aided by symbiotic bacteria. [68] There are two major genera of EPNs: Heterorhabditis and Steinernema, that are symbiotically associated with different species of bacteria of the genera Photorhabdus and Xenorhabdus, respectively. [69] Nematodes colonize their prey by entering through natural apertures or directly by breaking through the cuticle. [70] Then, the nematodes release their symbiotic bacteria that produce digestive enzymes, immune-suppressors, and toxins that kill the infected organism. [68,71] Nematodes feed on the resulting pre-digested tissues, reproduce, re-establish symbiosis, and abandon the cadavers in search for new prey. [70] Due to their living habitat and feeding habits, the performance and behavior of EPNs is directly and indirectly impacted by different environmental chemicals, including plant- and host-derived molecules. [72] and chemicals released by other organisms such as fungi. [73] In turn, due to the biosynthetic capacity of the nematodes and their bacterial symbionts, nematode- and bacteria-derived chemicals can also impact other soil-dwelling organisms, including plants, herbivore and predatory insects, and other nematodes. [74]

3.1 Impact of Plant- and Host-derived Volatiles on EPNs

EPNs need to locate a suitable prey to infect. In the case of ‘cruiser’ nematodes, the distribution of prey requires the nematode to disperse and crawl towards the prey. [75] Immersed into the soil matrix, with no visual cues, nematodes rely on olfaction and hence use different volatile cues to locate their prey. [76] The origin of these volatile cues is not limited to molecules emitted directly by their prey, but EPNs also perceive and respond to molecules that are associated with their future prey. [77] For instance, EPNs have evolved the capacity to respond to plant volatiles, perhaps as an adaptation to locate and infest herbivorous insects. [76c,78]

Several families of root-emitted volatiles from different plant species exert attractive or repellent effects on EPNs. [72d,79] Aromatics, aldehydes, alcohols, sesquiterpenes, benzenes, and ketones are often reported to attract, while sulfur-containing compounds repel nematodes. [76b,80] Nematode hosts also emit different behaviorally active volatiles. [76a,81] Several alcohols, aldehydes, ketones, and terpenes trigger nematode behavior. [72d] While most of them are either repellent or attractive, some of them can attract or repel depending on their concentration. [72d,82] For instance, ammonia released by nematode-infested insects is attractive at low concentrations but repellent at high concentrations.

There are two interesting aspects to highlight about volatile-regulated EPN behavior. First, most behaviorally active volatiles are highly species-specific. For instance, (E)-β-caryophyllene (22, Fig. 4) is exclusively produced and emitted by plants and attracts EPNs [73,83] while tert-butylation hydroxytoluene (23) is exclusively emitted by EPN-infected insects and also attracts nematodes. [72b] Other compounds like CO₂, hexanol, and α-pinene are emitted by both plants and insects, and can be attractive or repellent, depending on the dose. [76b,84] Second, the same molecules can be either neutral, attractive or repellent depending on the species of the responding nematode. [77a,77b,77c,77d,77e,77f,77g,77h,77i,77j,77k,77l,77m,77n,77o,77p,77q,77r,77s,77t,77u,77v,77w,77x,77y,77z] For instance, hexanol is attractive to S. carpocapsae but repels H. bacteriophora. [76b] Similarly, limonene, α-pinene, dimethyl disulfide, octanal and bornyl acetate induce contrasting behavioral responses in a nematode species-specific manner. [72d,76b,84b]

Compounds such as terpinolene are generally repellent and de- canal attractive to several nematode species. [76a] Taken together, nematodes tightly regulate their responses to the different environmental volatiles to optimize their foraging strategies.

3.2 Impact of Plant- and Host-derived Non-volatile Chemicals on EPNs

In contrast to volatiles, our understanding of how non-volatile plant- or host-derived metabolites influence EPN behavior is much less advanced. [72d,76b,86] In general, it is thought that root water-soluble metabolites have little effect on migration patterns and infectivity of EPNs. [87] However, the presence of certain plant species can alter host-finding abilities of EPNs. [88] For instance, roots alone are attractive to EPNs, and sometimes even more attractive than their...
Several water-soluble metabolites present in insect gut and feces, such as uric acid, influence EPN behavior. Ambusher nematodes, for instance, respond to host cues in a manner that suppresses the growth of EPN symbiotic bacteria, but have little effect on overall EPN infectivity. Similarly, pyrrolizidine alkaloids have been implied to confer resistance to EPNs, while little effects of cardenolides are observed. It remains to be determined if these effects can be driven by nematode adaptations. Indeed, EPNs that share an evolutionary history with WCR evolved resistance to benzoxazinoids. Whether EPNs have adapted to different plant-derived secondary metabolites remains to be determined.

3.3 Impact of EPN Symbiotic Bacteria-derived Molecules on other Organisms

The biosynthetic capacities of the symbiotic Xenorhabdus and Photorhabdus bacteria are unarguably enormous. The biological activity of these metabolites has been investigated for at least four decades and many bioactive molecules have been isolated and characterized. These molecules not only regulate the interaction between the bacteria, their nematode hosts, and their prey (insects), but can also impact other organisms. In the case of bacteria–nematode interactions, the bacteria produces molecules that regulate the nematode’s transition from the infective to the parasitic stage (‘infective juvenile recovery’). Little is known about the nature of these signals, termed also as ‘food signals’, but (E)-3,5-dihydroxy-4-isopropylstilbene is known to play a crucial role in this process. Interestingly, IPS also dampens insect immune responses and exhibits antibiotic properties. The bacteria also produce nutrients that are essential for nematode growth such as vitamins and proteins, or siderophores that increase the bioavailability of minerals such as iron.

Many more bacterial metabolites are thought to be relevant for nematode growth. Indeed, Photorhabdus mutants lacking the post-transcriptional global regulator Hiro are impaired in the production of several secondary metabolites, and do not support nematode growth. Hence, several yet to be discovered secondary metabolites could also play relevant roles in this context.

The interaction between Xenorhabdus and Photorhabdus bacteria and insects is largely mediated by proteins, rather than small molecular weight compounds. These proteins are often insecticide factors and include, for instance, toxic complex (Tc) toxins, make caterpillar floppy (MCF) toxins, Photorhabdus virulence cassettes (PVC), Photorhabdus insect-related toxins (PirAB), Galleria toxin (Galtox), and Photorhabdus asymbiotic toxins (PaTox).

Several Xenorhabdus and Photorhabdus metabolites also show potent antifungal, acaricidal, antibacterial, and nematocidal activity. Interestingly, EPN-infected cadavers emit a bouquet of different volatiles including 6-methoxy-2-benzoxazolinone upon nematode attack. These volatiles are important mediators of ecological interactions. Scavengers are reluctant to feed on nematode-infested cadavers. These volatiles are important mediators of ecological interactions. Scavengers are reluctant to feed on nematode-infested cadavers.

3.4 Impact of Chemicals Released by EPN-infested Insects on other Organisms

Once nematodes have colonized an insect prey, they release their symbiotic bacteria that, through the production of lytic enzymes, digest the insect tissues to facilitate nematode feeding. The phytochemical properties of the insects change dramatically, which is accomplished by the release of different volatile substances. These volatiles are important mediators of ecological interactions. Scavengers are reluctant to feed on nematode-infested cadavers. These efforts are thought to be driven by the chemical composition of the volatiles emitted by insect cadavers. Indeed, EPN-infected cadavers emit a bouquet of different volatiles including hexadecanal and 2-heptadecanone that are extremely repellent to Lasius niger scavenging ants. Interestingly, EPN-infected cadavers attract WCR larvae. Again, different volatiles are emitted.
by the cadavers, but butylated hydroxytoluene (BHT) sufficiently explains the attractive effects of nematode-infected cadavers.\textsuperscript{72b}

Interestingly, the attractive effects of BHT to WCR larvae were accompanied by an increased nematode reproductive output.\textsuperscript{72b}

The volatiles emitted by EPN-infested insects also impact plants.\textsuperscript{116a} For instance, when the roots of potato plants are exposed to EPN-infest cadavers, systemic defenses are induced that negatively influence both the performance and feeding preferences of Colorado potato beetles (CPB).\textsuperscript{116c} More specifically, CPB larvae consume less leaf tissue and gain less weight on plants exposed to EPN-infested insects than on control plants, and females lay fewer eggs on plants exposed to EPN cues than on control plants. Although the underlying mechanisms that regulate this fascinating phenomenon are generally poorly understood and deserve further attention, recent evidence shows that exposing the roots to EPNs suppresses polyphenol oxidase and guaiacol peroxidase activity in the leaves, which is accompanied by increased performance of leaf miner insects.\textsuperscript{116a,b} Exploring these phenomena at the mechanistic levels constitute, indeed, exciting research avenues for the future.

4. Conclusions

Ongoing research over the last decade has revealed some of the nematode-produced small molecule signals and demonstrated how nematodes are affected by currently released by other organisms in their environment. Considering that nematodes represent the most abundant group of animals on Earth, our understanding of many ecosystems will clearly remain incomplete without considering their contributions. Our future advancement in the field of nematode chemical ecology will require a collaborative effort of ecologists and natural product chemists, which can be foreseen to result in many fascinating discoveries with potential impact on important fields of social and economical significance, including agriculture and healthcare.

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