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Chemical Ecology of Nematodes

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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

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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-dideoxysugar 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

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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;[11f,12a,d] d) as well as the modular assembly of additional building blocks derived from diverse primary metabolic pathways.[10e,h,j–l,11a,e,14] 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*.[10h,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,[10f,h] ESI-(–)-MS/MS precursor ion screening,[10k] screening for characteristic marker ions in GC-EIMS 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-ωC3 (ascr#5) control dauer development.[10c,i,m,18] Dauer activity of ascarosides is highly structure dependent.[10o,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-C9 (**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, ascarosides affect nematode behavior, by modulating attraction,[10i–k] aggregation,[10j] as well as avoidance and repulsion.[10a,d,14,25]

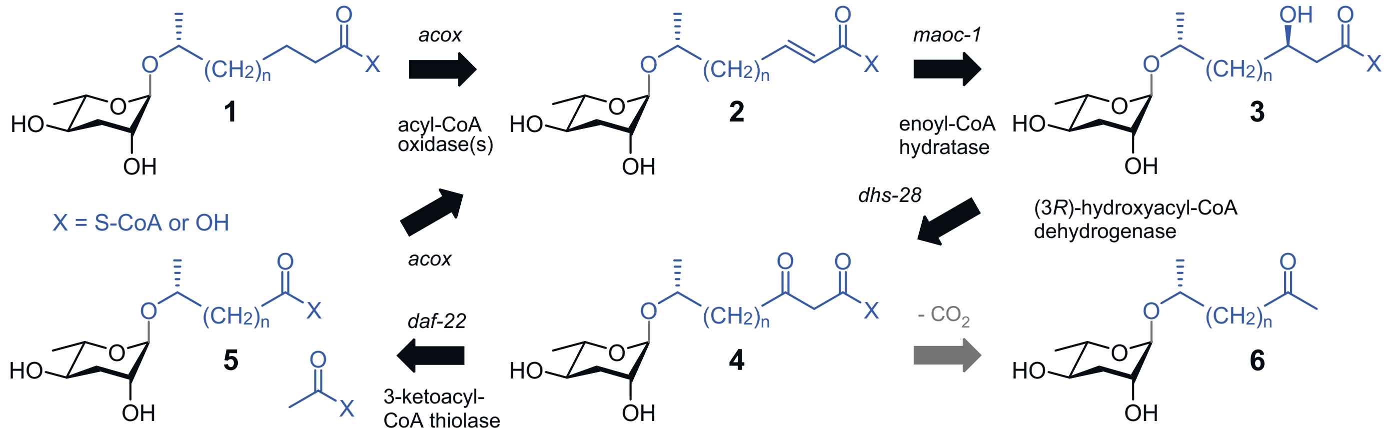

Fig. 1. Ascaroside biosynthesis *via* peroxisomal β-oxidation.

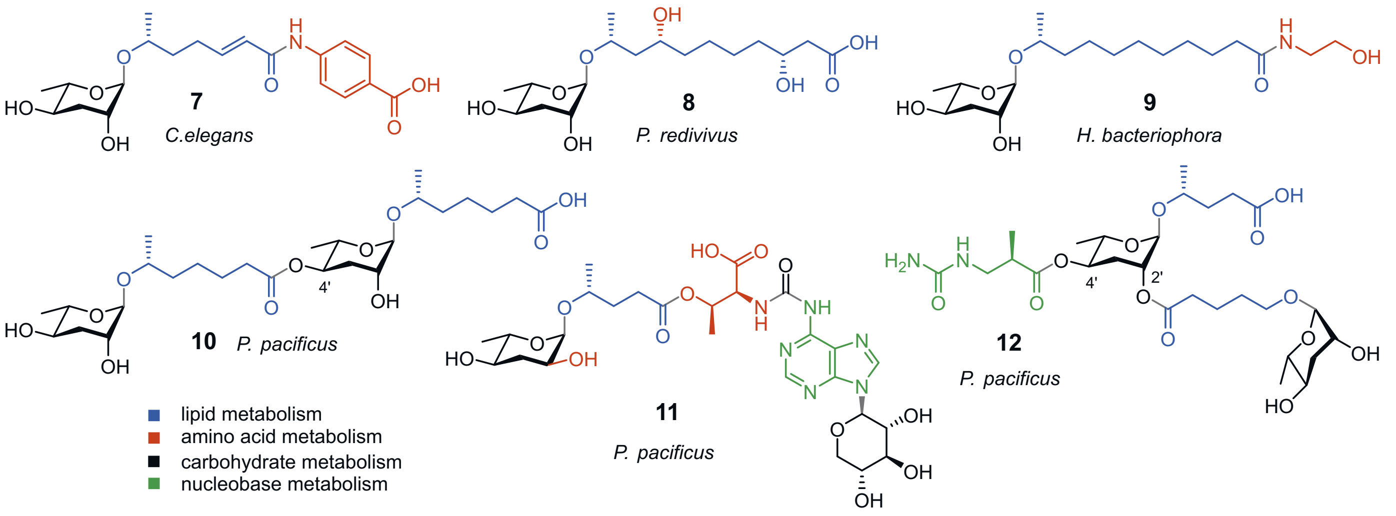

Fig. 2. Selection of species-specific ascarosides.

Similar ascaroside responses on nematode behavior and development have been characterized in other species. Males of gonochroristic *Caenorhabditis inopinata*, the sister species of *C. elegans*, are attractated to simple ascarosides.[1c] Males of the gonochoristic *Caenorhabditis remanei* and *Caenorhabditis nigoni* are exclusively retained by their conspecific ascaroside dimers.[11f] Males of *C. remanei* are retained by female-produced fatty acid ascarosides.[11e] Modular indole ascarosides act as attractants in various *Caenorhabditis* species.[11a] *C. elegans* shows the strongest retention to the conspecific asc-ΔC9-PABA (**7**, ascr#8) in comparison to various related *Caenorhabditis* species.[26]

Dauer development in hermaphroditic *Caenorhabditis briggsae* is regulated by asc-C6-MK (**6**, n = 2).[11g] 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*.[13] Males of the three-gendered *Auanema 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).[27] Asc-C5 (**1**, n = 0) influences reproductive plasticity in pine wilt nematode *Bursaphelenchus xylophilus*.[28] Entomopathogenic nematodes (EPNs) such as *Heterorhabditis* spp. and *Steinernema* spp. produce and respond to ascaroside signals,[29] which affect their recovery, yield, and dispersal.[30] Asc-C5 (**1**, n = 2) along with other yet unidentified components regulates EPN dispersal.[31] The ethanolamide asc-C11-EA (**9**) induces formation of infective juveniles in *Heterorhabditis bacteriophora*.[32] In *Pristionchus pacificus* dauer development and mouth form dimorphism that enable a predatory lifestyle are regulated by highly species-specific modular ascarosides dasc#1 (**10**) and npar#1 (**11**).[12a,c] Natural variation in dauer pheromone production and sensing suggests a role in intraspecific competition.[12b,c,33]

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

Ascarosides released by animal parasitic nematodes modulate host immune responses. Acute treatment with ascarosides improves hepatic inflammation in aged mice.[41] Ascarosides released by parasitic species, especially asc-ΔC7 (**2**, n = 2, ascr#7) attenuate mammalian type 2 inflammatory responses.[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.[43]

2.3 *Biosynthesis of Ascarosides*

Biosynthesis of the homologous ascaroside 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.[10k] Functions of acyl-CoA oxidases (*acox*),[10k,16b,44] enol-CoA hydratase (*maoc-1*),[10k,16b] 3-hydroxyacyl-CoA dehydrogenase (*dhs-28*),[10k,n,16b,45] and 3-ketoacyl-CoA thiolase (*daf-22*)[10b,f,h,k,n,16b,45] have been characterized. As expected for a canonical primary metabolic pathway, various orthologs have been identified in other nematodes. *Cbr-daf-22* from *C. briggsae* is required for production of short-chain ascarosides.[11g] *Bx-daf-22* contributes to mate attraction in gonochoristic *B. xylophilus*.[46] Two *Ppa-daf-22* paralogs from *Pristionchus pacificus* have been linked to dauer development.[47] *Hc-acox-1*,[48] *Hc-maoc-1*,[49] *Hc-dhs-28*,[50] and *Hc-daf-22*[51] orthologs have been characterized in *Haemonchus contortus* and linked to the regulation of diapause.[51b]

In contrast to the chain shortening of the aglycone during peroxisomal β-oxidation, the biosynthesis of the key 3,6-dideoxysugar, the L-ascarylose unit, has remained enigmatic. Ascaroside production in axenic media unambiguously established its nematode origin[10j] and several putative biosynthetic genes have been assigned, which, however, have been demonstrated to be linked to L-rhamnose biosynthesis.[52]

Combination of comparative metabolomics and genome-wide association mapping (GWAS) with multiple *Pristionchus pacificus* strains revealed a carboxylesterase (*Ppa-uar-1*) involved in biogenesis of modular ascarosides like ubas#1 (**12**).[12e] Subsequently, an orthologous family of carboxylesterases (CEST) enzymes localized in lysosome related organelles (LROs) has been characterized in *C. elegans* and shown to be involved in the biogenesis of various modular ascarosides.[17a,53]

Ascaroside signals present in the nematode's environment are taken up and further metabolized by β-oxidation and attachment of additional building blocks.[10j,k,p,q] Metabolism of medium-chain ascarosides has been explored by feeding [$^{13}C_2$]-labelled ascarosides[17b] or alkyne-labelled derivatives for click-chemistry-based enrichment of the corresponding metabolites.[54] Furthermore, nematode-derived ascarosides are also edited by plants,[55] fungi, bacteria, and mammals.[17b] Activated biosynthetic acyl-*S*-CoA intermediates have been tagged by reaction with $^{14}NH_2OH$.[56]

Ascaroside biosynthesis is highly species-specific and depends on the nematode's sex[10g,11e,13,27] and developmental stage,[10a,b,57] as well as the nutritional state[10a,b,k,p,21,57] and the bacterial food source(s)[11e] of the producing organism. Ascaroside production is upregulated by temperature stress *via* the heat-shock transcription factor *hsf-1*.[58]

Ascaroside production in entomopathogenic *Steinernema* spp. is largely independent of symbiotic versus non-symbiotic bacteria.[59] In contrast, indole ascarosides in bacterivorous *C. elegans* depend on the availability of L-tryptophan within the bacterial diet and thereby link nematode aggregation behavior to nutritional status.[10j,q] 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.[11e]

2.4 *Other Signaling Molecules from Nematodes*

Whereas our current understanding of nematode effectors suggests an outstanding importance of ascaroside 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 (2*E*,4*Z*,7*Z*)-*N*-decatrienoyl-glutamine (nacq#1) (**13**) promotes dauer recovery in hermaphrodites and accelerates larval development.[60] Indole-*N*-glucoside (iglu#1) (**14**) represents a detoxification product of *E. coli*-derived indole.[61] Anthranilic acid glucoside (angl#1) (**15**) is accumulated in LROs and released upon nematode death.[62] Based on these and other glucosides a diverse library of modular glucosides (mogl) (**16**) is accumulated in the *C. elegans* endometabolome, especially upon starvation.[17a,c] The nemamides (**17**) represent the first (and only) mixed PKS-NRPS metabolites produced by multicellular organisms and promote survival during starvation-induced larval arrest.[63] Sulfolipids (**18**) are released upon rupture of nematodes and serve as alarm pheromones.[64] The lipophilic polyunsaturated wax ester nematoil (**19**) facilitates nematode aggregation to form 'towers' involved in phoresy.[65] Homologous maradolipids (**20**) with a 6,6'-diacyltrehalose core structure are exclusively produced

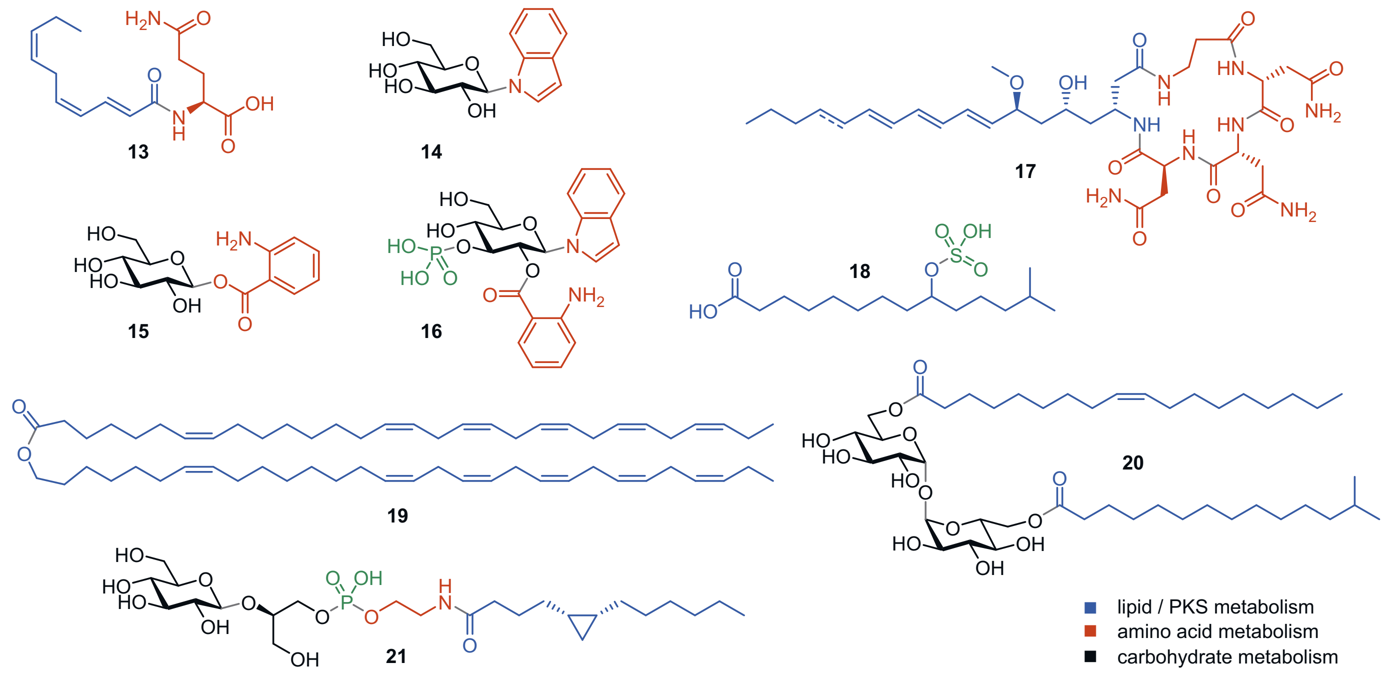

Fig. 3. Nematode-derived secondary metabolites.

in the dauer stage but their function remains unknown.[66] Several homologous *N*-acyl phosphoethanolamine (**21**) have been identified in *C. elegans*.[17d,67] 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] For instance, ammonia released by nematode-infested insects is attractive at low concentrations but repellent at high concentrations.[82]

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,[77a,83] while *tert*-butylated hydroxytoluene (**23**) is exclusively emitted by EPN-infected insects and also attracts nematodes.[72b] Other compounds like CO_2, 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,85] 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 decanal 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,d,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

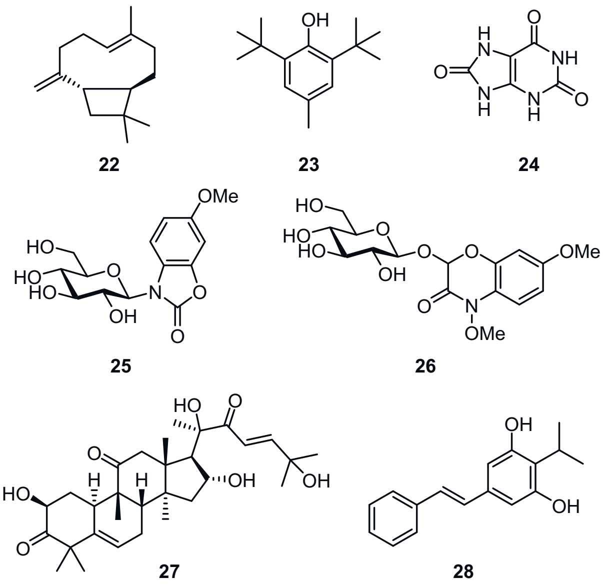

Fig. 4. Small molecule signals affecting EPNs.

own host, but the presence of insects close to the roots can mask the attractive effects of roots, depending on the species and foraging habit of the responding nematode.[88,89] Rhizo-depositions are rich in organic acids, amino acids, and sugars.[90] However, compared to their effects on phytopathogenic nematodes, it remains poorly investigated how these metabolites influence EPN behavior.[91] Root exudates of green pea and maize induce reversible quiescence in several EPN species at high concentrations and enhances EPN infectivity at low concentrations.[92] It is therefore likely that many other root exudates influence different EPN life traits.

EPNs respond differently to volatile and non-volatile insect-derived molecules depending on the EPN foraging strategy.[93] Ambusher nematodes, for instance, respond to host cues in a hierarchical order, with host volatile cues being more important after the nematode made contact with insect-derived contact cues, whereas volatile cues are more important for cruiser nematodes.[93] Several water-soluble metabolites present in insect gut and feces such as uric acid (**24**) and arginine attract EPNs while allantoic acid acts as a repellent.[80b,87c,94] In addition, insect diet strongly influences EPN infectivity.[95] These effects are hypothesized to be driven by plant secondary metabolites.[95] Indeed, plant-derived metabolites such as benzoxazinoids that are sequestered and/or metabolized by herbivorous insects strongly influence EPNs and their symbionts.[69a,72a,c,96] Benzoxazinoids are multifunctional plant metabolites produced by poaceous plants that are used as defense against herbivores, to optimize nutrient uptake, and to shape root microbiota, among others.[97]

Certain highly specialized insects such as the Western Corn Rootworm (WCR) are fully tolerant to these toxins and have evolved the capacity to selectively accumulate them and even use them against natural enemies, including EPNs, increasing their resistance.[69a,72a,c,96] The increased resistance is associated with two different mechanisms. First, the insect at the larval stages exude 6-methoxy-2-benzoxazolinone *N*-glucoside (MBOA-Glc) (**25**), which repels foraging EPNs.[72a] Second, the larvae accumulate 2-hydroxy-4,7-dimethoxy-1,4-benzoxazin-3-one *O*-glucoside (HDMBOA-Glc) (**26**) and release its breakdown product 6-methoxy-2-benzoxazolinone (MBOA) upon nematode attack.[96] These two compounds directly reduce the survival of the nematode and their *Photorhabdus* bacterial symbionts.[72a,c,96] Benzoxazinoids are not the only plant-derived metabolites that influence EPNs and their symbionts. Cucurbitacins like Cucurbitacin D suppress the growth of EPN symbiotic bacteria, but have little effect on overall EPN infectivity.[97] Similarly, pyrrolizidine alkaloids have been implied to confer resistance to EPNs,[99] while little effects of cardenolides are observed.[100] 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.[72a] 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.[101] The biological activity of these metabolites has been investigated for at least four decades[102] and many bioactive molecules have been isolated and characterized.[103] 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').[104] Little is known about the nature of these signals, termed also as 'food signals', but (*E*)-3,5-dihydroxy-4-isopropylstilbene (**28**, IPS) has been shown to play a crucial role in this process.[105] Interestingly, IPS also dampens insect immune responses and exhibits antibiotic properties.[102,106] 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.[107] Many more bacterial metabolites are thought to be relevant for nematode growth. Indeed, *Photorhabdus* mutants lacking the post-transcriptional global regulator *Hfq* are impaired in the production of several secondary metabolites, and do not support nematode growth.[108] Hence, several yet to be discovered secondary metabolites could also play relevant roles in this context.[109]

The interaction between *Xenorhabdus* and *Photorhabdus* bacteria and insects is largely mediated by proteins, rather than small molecular weight compounds.[110] 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 asymbiotica* toxins (PaTox).[71a,111]

Several *Xenorhabdus* and *Photorhabdus* metabolites also show potent antifungal, acaricidal, antibacterial, and nematicidal activity.[101a,b,102,109b,112] This is the case for 3,5-dihydroxy-4-isopropylstilbene, carbapenem, anthraquinone-derivatives, abclavines, xenocoumacins, xenorhabdins and PAX peptides.[103] Apart from these, *Photorhabdus* bacteria also produce other bioactive molecules such as the phytohormones auxins and gibberellins, as well as volatiles that positively influence plant growth and plant defense against herbivorous pests.[113] The potential of *Photorhabdus* and *Xenorhabdus* metabolites to regulate complex ecological interactions warrants therefore further research efforts.

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 physiochemical properties of the insects change dramatically, which is accompanied by the release of different volatile substances. These volatiles are important mediators of ecological interactions. Scavengers are reluctant to feed on nematode-infested cadavers.[114] These effects are thought to be driven by the chemical composition of the volatiles emitted by insect cadavers.[115] Indeed, EPN-infected cadavers emit a bouquet of different volatiles including hexadecanal and 2-heptadecanone[74b] that are extremely repellent to *Lasius niger* scavenging ants.[74b] 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.[72b] Interestingly, the attractive effects of BHT to WCR larvae were accompanied by an increased nematode reproductive output.[72b]

The volatiles emitted by EPN-infested insects also impact plants.[116] For instance, when the roots of potato plants are exposed to EPN-insect cadavers, systemic defenses are induced that negatively influence both the performance and feeding preferences of Colorado potato beetles (CPB).[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.[116e] 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 directly affected by cues 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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