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Chemical host-seeking cues of entomopathogenic nematodes

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Entomopathogenic nematodes (EPNs) are obligate parasites that infect a broad range of insect species. Host-seeking is a crucial step for EPN infection success and survival. Yet, the identity and ecological functions of chemicals involved in host-seeking by EPNs remain overlooked. In this review, we report known CO₂, plant-derived and insect-derived cues shaping EPN host-seeking and recognition. Despite species-specific response to environmental cues, we highlight a hierarchical integration of chemicals by EPNs. We further emphasize the impact of EPN selection pressure, age, and experience on their responsiveness to infochemicals. Finally, we feature that EPN chemical ecology can translate into powerful sustainable strategies to control insect herbivores in agriculture.

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Introduction

Entomopathogenic nematodes (EPNs) are obligate parasites that infect and kill insects. Their short life cycles, simple rearing requirements, and straightforward molecular manipulations render them ideal to study host–parasite interactions [1]. Additionally, their efficacy in reducing herbivore damage in the field contributed to their use as biological control agents in agriculture [2[•],3].

EPNs comprise three genera, *Heterorhabditis*, *Steinernema*, and *Oscheius* [4]. Infective juveniles (IJs) are third-stage free-living nematode larvae (iL3) that locate, select, and infect a host by entering through a natural orifice or by penetrating through the cuticle. Upon infection, IJs release venom proteins and regurgitate an endosymbiotic entomopathogenic bacterium, leading to a fatal toxemia and septicemia of the host. Juveniles then undergo a transition from free-living to parasitic lifestyle and resume growth and development by feeding on the infected flesh. Adult nematodes reproduce inside the host generating several new generations of nematodes [5]. Resource depletion and elevated nematode densities induce the production of ascaroside C11 ethanolamine, an ascaroside triggering the production of next generation IJs, often through *Endotokia matricida* [6]. The newly hatched IJs emerge from the resource-depleted host and search to infect new hosts.

Juvenile host-seeking strategies are typically classified along a gradient ranging from ambushing to cruising [7]. Ambusher nematodes are stationary and infect mobile hosts. Attachment to a mobile host can be achieved through nictation, which corresponds to the nematode standing on its tail, curling, and propelling itself in the air [8]. Cruiser nematodes disperse in the soil and locate sedentary hosts [9]. Nematodes with intermediate strategies can ambush or disperse depending on the soil matrix and host presence [10,11]. Additionally, recent studies highlighted that EPNs can attract insects to infected cadavers just before emergence [12^{••},13[•]]. Being the first step of host–parasite interactions, host-seeking is critical in determining the success of a parasite.

The cues shaping host-seeking can be physical and chemical [14]. Olfactory cues trigger chemotaxis or nictation in all tested EPN species, and include carbon dioxide, as well as specific host-derived and plant-derived chemicals. EPNs may use CO₂ gradients to locate biological activity, herbivore-induced plant volatiles to locate herbivore insects from a distance, and insect-derived chemicals to accurately find a host. Finally, EPNs can assess their host quality, including infection status or diet, prior infection. Yet, and despite their pivotal role in host–parasite interaction, the identity and ecological functions of the chemicals involved in host-seeking and host-recognition by EPNs remain poorly understood [15].

In this review, we gather knowledge about chemical signals involved in EPN host-seeking and host-recognition behavior. We highlight the connection between the type of chemicals used for foraging and EPN specialization degree, foraging strategy, development, and experience. Finally, we feature how EPN chemical ecology can translate into sustainable pest management strategies.

Infochemicals shaping EPN host-seeking

Carbon dioxide

EPNs can use CO₂, ubiquitously emitted by most living organisms, for host location (for review see Ref. [16^{••}]). CO₂ triggers foraging by EPNs with divergent life strategies, for example, generalists, specialists, ambushers, and cruisers, each of them exhibiting different sensitivity to this cue [17[•],18]. The CO₂ response is mediated through the paired BAG sensory neurons of the head in nematodes [18,19]. By elegantly combining BAG-neuron ablation and CO₂-free attraction assays, Hallem *et al.* demonstrated that *H.* and *S. carpocapsae* can use CO₂ solely or in combination with insect or plant odors to locate a host [18,19].

Plant-derived cues

EPNs have evolved the ability to use plant signals to locate potential herbivore hosts. Herbivore-infested roots release a specific blend of molecules compared to healthy plants [20–22]. The abundance and diffusion of these herbivore-induced plant volatiles (HIPVs) represent a detectable, albeit not reliable, indicator of herbivore presence. Belowground olfactometer assays and real-time observations of EPN behavior in Pluronic gel demonstrate that EPNs aggregate in the vicinity of plant roots and preferentially orient towards wounded plants than towards healthy plants [23–25]. HIPVs from various plant species, including maize, citrus trees, potato, sugarcane, carrot and vine, induce chemotaxis in EPNs [20,21,26–32]. The attractive effect of HIPVs was observed in both cruiser and ambusher EPNs, but the response to different volatiles was strain-specific rather than related to EPN foraging strategies [30–33]. For example, only one strain out of 3 tested strains of the ambusher *S. carpocapsae* exhibit chemotaxis towards linalool [32]. Furthermore, some HIPVs can trigger the nictation of the ambusher [18]. An increasing number of chemical compounds mediating EPN host-seeking behavior have been identified and are summarized in Table 1.

Insect cues

EPNs can use insect-specific cues to efficiently locate a host [34,35]. Herbivores constantly release chemicals in their environment through pheromones, exudates, molting skins (exuviae), or feces (frass). Insect-derived chemicals diffusing in the soil matrix can trigger EPN attraction, repellence, or nictation (Table 2). Common insect cues triggering chemotaxis or nictation of EPNs include frass chemicals such as nitrogen metabolism, and waste

products, such as uric acid, hypoxanthine, xanthine, allantoin, urea, and ammonia [36]. Insect species-specific compounds, such as sex pheromones, can attract EPNs. For example, the feces of the adult citrus weevil, *Diaprepes abbreviatus*, contains [(*E*)-3-(2-hydroxyethyl)-4-methyl-2-pentenoate], a pheromone involved in female attraction for mating [37]. Intriguingly, this pheromone participates in the recruitment of two intermediate cruiser EPNs, *S. diaprepesi* and *H. indica* [38[•]]. Rivera *et al.* hypothesized that the pheromone-containing frass could be used as an indicator of a near-future egg deposition and host presence [38[•]]. The strength of chemotactic response to insect-derived cues mirrors EPN host-seeking strategies: Ambusher EPNs are less responsive to insect chemicals [17[•]], except if the latter are associated with air movement or physical contact with the potential host [39[•],40]. Known insect cues mediating EPN host-seeking are summarized in Table 2.

Infochemicals shaping EPN host-recognition

EPNs can use insect cues to recognize and assess the quality of a potential host. EPNs can distinguish between insects fed on different plant species [41], although the involved cues remain unidentified. EPNs may further recognize herbivores sequestering toxic plant secondary metabolites. For instance, EPNs are repelled by six-methoxy-2-benzoxazolinone-*N*-glucoside (MBOA-Glc), a plant benzoxazinoid detoxification product, released by the benzoxazinoid sequestering root herbivore, *Diabrotica virgifera* [42[•]]. Similarly, EPNs are repelled by glucosinolate breakdown products [43]. Although numerous specialist herbivores have evolved the ability to sequester and/or release toxic plant metabolites, the impact of the latter on EPN foraging remains overlooked [41,44]. Furthermore, EPNs can differentiate between healthy and infected hosts [13[•],45–48], and even between hosts infected with conspecific or heterospecific EPNs [49]. So far, only a few compounds, such as isoprenoid prenol (3-Methyl-2-buten-1-ol) and butylated hydroxytoluene (BHT), have been implicated in late infection recognition cues [12^{••},13[•]]. Interestingly, both prenol and BHT attract new, healthy, insects to late stage of infection cadavers, an effect that enhances the probability of emerging EPNs to encounter new hosts [12^{••},13[•]]. It should also be noted that, while prenol repels EPNs, BHT attracts IJs and enhance their predation success [12^{••}]. Known insect cues mediating EPN host-recognition are summarized in Table 2.

Interactive effects and hierarchical response to multiple cues

Although the most reliable cues for EPNs to forage would be cues emanating from potential hosts, the latter evolved to emit barely detectable amounts of signals [50]. On the other hand, attacked plants release large amounts, albeit less reliable, of chemicals that diffuse in the soil matrix [51]. This reliability-detectability dilemma may have driven EPNs to integrate a combination of CO₂, plant, and insect

Table 1

Plant-derived infochemicals involved in entomopathogenic nematode foraging

Compound effect on EPNs	EPN species	Chemical type	Compound	Plant species	Ref.
Attractive	<i>H. bacteriophora</i>	Aromatic	2,4-Di- <i>tert</i> -butylphenol	Carrot (<i>Daucus carota</i>)	[30]
Attractive	<i>H. bacteriophora</i>	Aldehyde	Decanal	Potato (<i>Solanum tuberosum</i>)	[31]
Attractive	<i>H. bacteriophora</i>	Aldehyde	Octanal	Potato (<i>Solanum tuberosum</i>)	[31]
Attractive	<i>H. bacteriophora</i>	Alcohol	1-Octanol	ND	[56]
Attractive	<i>H. bacteriophora</i>	Alcohol	1-Nonanol	ND	[56]
Attractive	<i>H. bacteriophora</i>	Alcohol	2-Heptanol	ND	[56]
Attractive	<i>H. bacteriophora</i>	Sesqui-terpene	Humulene	Beech (<i>Fagus sylvatica</i>)	[26]
Attractive	<i>H. bacteriophora</i>	Benzene	p-Cymene	ND	[18]
Attractive	<i>H. bacteriophora</i>	Ester	Methyl salicylate	ND	[18]
Attractive	<i>H. megidis</i>	Alcohol	1-Octen-3-ol	Red fescue (<i>Festuca rubra</i>)	[28]
Attractive	<i>H. megidis</i>	Ketone	3-Octanone	Red fescue (<i>Festuca rubra</i>)	[28]
Attractive	<i>H. megidis</i>	Hydro-carbon	1-Undecene	Red fescue (<i>Festuca rubra</i>)	[28]
Attractive	<i>H. megidis</i>	Hydro-carbon	Nonadecatriene	Red fescue (<i>Festuca rubra</i>)	[28]
Attractive	<i>H. megidis</i>	Sesqui-terpene	α -Curcumene	Red fescue (<i>Festuca rubra</i>)	[28]
Attractive	<i>H. megidis</i>	Sesqui-terpene	(<i>E</i>)- β -Caryophyllene	Maize (<i>Zea mays</i>)	[21]
Attractive	<i>H. megidis</i>	Disulfide	Dimethyl disulfide	Black mustard (<i>Brassica napus</i>)	[52]
Attractive	<i>S. carpocapsae</i>	Alcohol	Octanol	ND	[18]
Attractive	<i>S. carpocapsae</i>	Alcohol	Nonanol	ND	[18]
Attractive	<i>S. carpocapsae</i>	Sesqui-terpene	(<i>E</i>)- β -Caryophyllene	Maize (<i>Zea mays</i>)	[32]
Attractive	<i>S. carpocapsae</i>	Mono-terpene	Linalool	Maize (<i>Zea mays</i>)	[32]
Attractive	<i>S. carpocapsae</i>	Mono-terpene	Bornyl acetate	Carrot (<i>Daucus carota</i>)	[30]
Attractive	<i>S. carpocapsae</i>	Aldehyde	Nonanal	Potato (<i>Solanum tuberosum</i>)	[31]
Attractive	<i>S. carpocapsae</i>	Aldehyde	Octanal	Potato (<i>Solanum tuberosum</i>)	[31]
Attractive	<i>S. carpocapsae</i>	Aromatic	1,2,4-Trimethylbenzene	Potato (<i>Solanum tuberosum</i>)	[31]
Attractive	<i>S. carpocapsae</i>	Ketone	2-Nonanone	ND	[18]
Attractive	<i>S. carpocapsae</i>	Alcohol	Heptanol	ND	[18]
Attractive	<i>S. carpocapsae</i>	Alcohol	Pentanol	ND	[18]
Attractive	<i>S. carpocapsae</i>	Sesqui-terpene	(<i>E</i>)- β -Caryophyllene*	Hemp varieties (<i>Cannabis sativa</i>)	[29]
Attractive	<i>S. carpocapsae</i>	Alcohol	Hexanol	ND	[18]
Attractive	<i>S. carpocapsae</i>	Ester	Octyl acetate	ND	[18]
Attractive	<i>S. diaprepesi</i>	Sesqui-terpene	Geijerene	Citrus (<i>Citrus paradisi</i> \times <i>Poncirus trifoliata</i>)	[20]
Attractive	<i>S. diaprepesi</i>	Sesqui-terpene	Pregeijerene	Citrus (<i>Citrus paradisi</i> \times <i>Poncirus trifoliata</i>)	[20]
Attractive	<i>S. diaprepesi</i>	Sesqui-terpene	α -Santalene	Citrus (<i>Citrus paradisi</i> \times <i>Poncirus trifoliata</i>)	[20]
Attractive	<i>S. diaprepesi</i>	Mono-terpene	α - <i>cis</i> -Bergamotene	Citrus (<i>Citrus paradisi</i> \times <i>Poncirus trifoliata</i>)	[20]
Attractive	<i>S. diaprepesi</i>	Mono-terpene	Limonene	Citrus (<i>Citrus paradisi</i> \times <i>Poncirus trifoliata</i>)	[27]
Attractive	<i>S. feltiae</i>	Aromatic	1,2,4-Trimethylbenzene	Potato (<i>Solanum tuberosum</i>)	[31]
Attractive	<i>S. feltiae</i>	Canna-binoid	Cannabidiol*	Medical cannabis (<i>Cannabis sativa</i>)	[29]
Attractive	<i>S. kraussei</i>	Aldehyde	Decanal	Potato (<i>Solanum tuberosum</i>)	[31]
Repellent	<i>H. bacteriophora</i>	Mono-terpene	α -Pinene	Carrot (<i>Daucus carota</i>)	[30]
Repellent	<i>H. bacteriophora</i>	Mono-terpene	Terpinolene	Carrot (<i>Daucus carota</i>)	[30]
Repellent	<i>H. bacteriophora</i>	Alcohol	Hexanol	ND	[18]
Repellent	<i>H. bacteriophora</i>	Alcohol	Heptanol	ND	[18]
Repellent	<i>H. bacteriophora</i>	Alcohol	Nonanol	ND	[18]
Repellent	<i>H. bacteriophora</i>	Alcohol	Octanol	ND	[18]
Repellent	<i>H. bacteriophora</i>	Aromatic	Belzaldehyde	ND	[18]
Repellent	<i>H. bacteriophora</i>	Mono-terpene	3-Carene	ND	[18]
Repellent	<i>H. bacteriophora</i>	Mono-terpene	Limonene	ND	[18]
Repellent	<i>H. megidis</i>	Hydro-carbon	Decane	Red fescue (<i>Festuca rubra</i>)	[28]
Repellent	<i>S. carpocapsae</i>	Mono-terpene	Terpinolene	Carrot (<i>Daucus carota</i>)	[30]
Repellent	<i>S. carpocapsae</i>	Mono-terpene	α -Pinene	Carrot (<i>Daucus carota</i>)	[30]
Repellent	<i>S. carpocapsae</i>	Alcohol	2-Ethylhexanol	Carrot (<i>Daucus carota</i>)	[30]
Repellent	<i>S. carpocapsae</i>	Mono-terpene	Bornyl acetate	Carrot (<i>Daucus carota</i>)	[30]
Repellent	<i>S. carpocapsae</i>	Alcohol	2-Ethyl-1-hexanol	Potato (<i>Solanum tuberosum</i>)	[31]
Repellent	<i>S. carpocapsae</i>	Mono-terpene	Limonene	ND	[18]
Repellent	<i>S. feltiae</i>	Aldehyde	Decanal	Potato (<i>Solanum tuberosum</i>)	[33]
Repellent	<i>S. feltiae</i>	Sulfide	Dimethyl sulfide	Black mustard (<i>Brassica napus</i>)	[43]
Repellent	<i>S. feltiae</i>	Aldehyde	Octanal	Potato (<i>Solanum tuberosum</i>)	[32]
Repellent	<i>S. feltiae</i>	Mono-terpene	Terpinolene	Carrot (<i>Daucus carota</i>)	[30]
Repellent	<i>S. feltiae</i>	Aldehyde	Octanal	Potato (<i>Solanum tuberosum</i>)	[30]
Repellent	<i>S. feltiae</i>	Hydro-carbon	Undecane	Potato (<i>Solanum tuberosum</i>)	[31]
Repellent	<i>S. kraussei</i>	Sulfide	Dimethyl sulfide	Black mustard (<i>Brassica napus</i>)	[43]
Repellent	<i>S. kraussei</i>	Disulfide	Dimethyl disulfide	Black mustard (<i>Brassica napus</i>)	[43]
Repellent	<i>S. kraussei</i>	Trisulfide	Dimethyl trisulfide	Black mustard (<i>Brassica napus</i>)	[43]
Repellent	<i>S. kraussei</i>	Isothio-cyanate	Allyl isothio-cyanate	Black mustard (<i>Brassica napus</i>)	[43]

Table 1 (Continued)

Compound effect on EPNs	EPN species	Chemical type	Compound	Plant species	Ref.
Repellent	<i>S. kraussei</i>	Isothio-cyanate	Phenylethyl isothiocyanate	Black mustard (<i>Brassica napus</i>)	[43]
Repellent	<i>S. kraussei</i>	Aromatic	Benzonitrile	Black mustard (<i>Brassica napus</i>)	[43]
Repellent	<i>S. kraussei</i>	Aromatic	2,4-Di- <i>tert</i> -butylphenol	Carrot (<i>Daucus carota</i>)	[30]
Repellent	<i>S. kraussei</i>	Mono-terpene	α -Pinene	Carrot (<i>Daucus carota</i>)	[30]
Repellent	<i>S. kraussei</i>	Mono-terpene	Terpinolene	Carrot (<i>Daucus carota</i>)	[30]

H.: *Heterorhabditis*; *S.*: *Steinernema*; *O.*: *Oscheius*. Ref.:reference. ND: Non determined, the authors used synthetic compounds that are known to be released by plants. A star indicates a putative effect, as the effect of the pure compound was not tested.

signals when foraging [50] (Figure 1). Yet, it would not be surprising if specialist EPNs respond to lower detection threshold for insect cues and almost exclusively rely on the latter, but this hypothesis remains to be tested. Some evidence points towards a hierarchical order of EPN response to specific stimuli during foraging. Cruiser EPNs preferentially orient towards a combination of CO₂ with plant or insect signals than towards individual signals [17*,52]. Similarly, they preferentially navigate towards plant and insect volatile combination rather than towards one of the signals alone [53]. Interestingly, EPNs preferentially follow plant volatile cues rather than herbivore odors alone [17*,20,53–56] although they prefer infested plant cues rather than healthy plant cues [25,57]. Finally, EPNs preferentially follow host-specific cues rather than CO₂ alone [17*,56] (Figure 1). Ambusher EPNs also follow a hierarchical order of response to environmental cues, but the required activation step may be physical (air movement, attachment to the insect cuticle) and not chemical [8,39*]. Understanding the order and combinations of stimuli used by EPNs during foraging is crucial to correctly identify involved infochemicals.

EPN species-specific response to infochemicals

EPNs exhibit species-specific response to CO₂, plant and insect cues. The relative importance of CO₂ is highly variable among species [16**]. It should be noted that the specialist EPN, *S. scapterisci*, relies less on CO₂ than generalist EPNs in the presence of host cues [17*,58]. Different EPN species exhibit strong preferences for different plant species [25,54,55], but whether these preferences correlate with the presence of their preferred hosts remains to be elucidated. Similarly, EPN response to insect cues varies considerably between EPN species. In a comprehensive chemotaxis and nictation study, Dillman *et al.* [17*] demonstrated that 4 out of the 6 tested species displayed specific responses to insect-derived cues [17*]. The specificity of response is a pivotal factor to account for when introducing EPNs for biological control. Several studies reported the inadequacy of introducing new EPN species to control herbivore pests [59], but understanding EPN-host specificity would allow to better define the appropriated strains to use.

Ecosystem-specific selection pressure, age, and experience shape EPN response to infochemicals

One of the challenges associated with the identification of chemical cues involved in EPN host-seeking behavior is the variability of response within strains. EPN response depends on their selection pressure, age, and experience. Artificial selection increases EPN host-finding efficacy within a few generations [60–62]. This rapid genetic adaptation of EPNs to environmental infochemicals together with low mobility suggest probably strong variations in chemotaxis between EPN populations [63].

Additionally, EPN age (referring here to the time since emergence from the natal cadaver) is implicated in behavioral shifts. For instance, CO₂ repels *S. scapterisci* IJs immediately after emergence but attracts them over the following weeks [64]. Similarly, the repellent effect of prenilol was age-dependent in 3 out of 5 tested EPN species [65].

EPN experience, through prior exposure to volatiles, can prime EPNs in a compound-specific manner [63], resulting in increased EPN efficacy [66*,67,68]. Persistent exposure results in increased preferences and long-term memory [63]. Intriguingly, primed EPNs can influence the behavior and chemotaxis of co-occurring EPN species [63]. The specificity of response to chemical cues emphasizes the crucial need for standardized assays to elucidate the role of infochemicals in host-seeking.

Chemically mediated interactions among EPNs and soil-living organisms

Except for herbivores, EPNs will also encounter and interact with various organisms in soil. EPNs may infect non-herbivore preys, such as fungivorous insects. It is probable that EPNs have evolved to recognize and orient towards fungal chemicals, and maybe even towards fungivore-induced fungal cues. Recently, 1-octen-3-ol (octenol) and 1-pentanol have been identified from the fungus *Fusarium solani* volatiles, which are attractive for both a fungivorous insect and for EPNs [18,69–71]. Other fungi, such as *F. oxysporum*, produce caryophyllene, which may

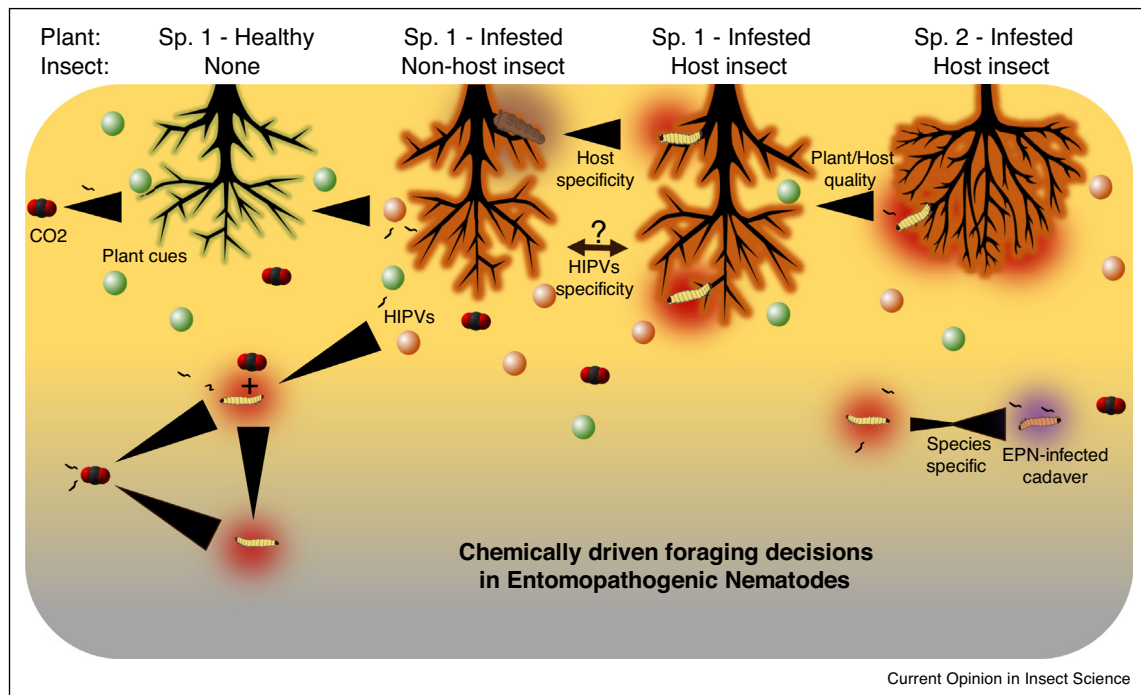
Table 2

Insect-derived infochemicals involved in entomopathogenic nematode foraging

Compound effect on EPNs	EPN species	Chemical type	Compound	Insect species	Ref.
Attractive	<i>H. bacteriophora</i>	Alcohol	Propanol	<i>Acheta domesticus</i> (Orthoptera)	[17*,18]
Attractive	<i>H. bacteriophora</i>	Thiazole	4,5 Dimethyl-thiazole	<i>Zophobas morio</i> (Coleoptera)	[18]
Attractive	<i>H. bacteriophora</i>	Oxide	Carbon dioxide	ND	[56]
Attractive	<i>H. bacteriophora</i>	Aromatic	Butylated hydroxytoluene	<i>Diabrotica virgifera</i> (Coleoptera)	[12**]
Attractive	<i>H. indica</i>	Ester	(E)-3-(2-Hydroxyethyl)-4-methyl-2-pentenoate	<i>Diaprepes abbreviatus</i> (Coleoptera)	[38*]
Attractive	<i>O. carolinensis</i>	Amine	Trimethylamine	<i>Acheta domesticus</i> (Orthoptera)	[17*]
Attractive	<i>O. carolinensis</i>	Mono-terpene	γ -Terpinene	<i>Acheta domesticus</i> (Orthoptera)	[17*]
Attractive	<i>O. carolinensis</i>	Amine	Trimethylamine	<i>Armadillidium vulgare</i> (Isopoda)	[17*]
Attractive	<i>O. carolinensis</i>	Aldehyde	Hexanal	<i>Galleria mellonella</i> (Lepidoptera)	[17*]
Attractive	<i>S. carpocapsae</i>	Ketone	2-Propanone	<i>Armadillidium vulgare</i> (Isopoda)	[17*]
Attractive	<i>S. carpocapsae</i>	Hydro-carbon	Tetradecane	<i>Armadillidium vulgare</i> (Isopoda)	[17*]
Attractive	<i>S. carpocapsae</i>	Ketone	2-Propanone	<i>Chrysobothris mali</i> (Coleoptera)	[17*]
Attractive	<i>S. carpocapsae</i>	Ether	Tetrahydrofuran	<i>Euborellia femoralis</i> (Dermaptera)	[17*]
Attractive	<i>S. carpocapsae</i>	Mono-terpene	α -Pinene	<i>Galleria mellonella</i> (Lepidoptera)	[17*]
Attractive	<i>S. carpocapsae</i>	Aromatic	4-Methylphenol	<i>Scapteriscus borellii</i> (Orthoptera)	[17*]
Attractive	<i>S. carpocapsae</i>	Quinone	p-Benzoquinone	<i>Scapteriscus borellii</i> (Orthoptera)	[17*]
Attractive	<i>S. carpocapsae</i>	Alcohol	Hexanol	<i>Galleria mellonella</i> (Lepidoptera)	[18]
Attractive	<i>S. carpocapsae</i>	Oxide	Carbon dioxide	<i>Tenebrio molitor</i> (Coleoptera)	[18]
Attractive	<i>S. carpocapsae</i>	Thiazole	4,5-Dimethylthiazole	<i>Zophobas morio</i> (Coleoptera)	[18]
Attractive	<i>S. diaprepesi</i>	Ester	(E)-3-(2-Hydroxyethyl)-4-methyl-2-pentenoate	<i>Diaprepes abbreviatus</i> (Coleoptera)	[38*]
Attractive	<i>S. feltiae</i>	Diureide	Allantoin	<i>Galleria mellonella</i> (Lepidoptera)	[36]
Attractive	<i>S. feltiae</i>	Hydride	Ammonia	<i>Galleria mellonella</i> (Lepidoptera)	[36]
Attractive	<i>S. feltiae</i>	Amino acid	Arginine	<i>Galleria mellonella</i> (Lepidoptera)	[36]
Attractive	<i>S. feltiae</i>	Purine	Uric acid	<i>Galleria mellonella</i> (Lepidoptera)	[36]
Attractive	<i>S. feltiae</i>	Purine	Xanthine	<i>Galleria mellonella</i> (Lepidoptera)	[36]
Attractive	<i>S. glaseri</i>	Amine	Trimethylamine	<i>Acheta domesticus</i> (Orthoptera)	[17*]
Attractive	<i>S. glaseri</i>	Amine	Trimethylamine	<i>Armadillidium vulgare</i> (Isopoda)	[17*]
Attractive	<i>S. glaseri</i>	Quinone	p-Benzoquinone	<i>Scapteriscus borellii</i> (Orthoptera)	[17*]
Attractive	<i>S. glaseri</i>	Hemi-terpene	Isoprenol	<i>Plodia interpunctella</i> (Lepidoptera)	[47]
Attractive	<i>S. scapterisci</i>	Hydroxy ketone	3-Hydroxy-2-butanone	<i>Acheta domesticus</i> (Orthoptera)	[17*]
Attractive	<i>S. scapterisci</i>	Sulfone	Dimethyl sulfone	<i>Acheta domesticus</i> (Orthoptera)	[17*]
Attractive/Repellent	<i>H. bacteriophora</i>	Hydride	Ammonia	<i>Galleria mellonella</i> (Lepidoptera)	[48]
Repellent	<i>H. bacteriophora</i>	Benzoxa-zolinone	MBOA-Glucose	<i>Diabrotica virgifera</i> (Coleoptera)	[42*]
Repellent	<i>H. bacteriophora</i>	Aldehyde	Hexanal	ND	[18]
Repellent	<i>H. bacteriophora</i>	Mono-terpene	α -Pinene	ND	[18]
Repellent	<i>H. bacteriophora</i>	Ketone	2,4-Butanedione	ND	[18]
Repellent	<i>S. carpocapsae</i>	Aldehyde	Hexanal	ND	[18]
Repellent	<i>S. carpocapsae</i>	Ketone	2,3-Butanedione	ND	[18]
Repellent	<i>S. feltiae</i>	Diureide	Allantoic acid	<i>Galleria mellonella</i> (Lepidoptera)	[36]
Repellent	<i>S. glaseri</i>	Hemi-terpene	Prenol	<i>Galleria mellonella</i> (Lepidoptera)	[13*]
Repellent	<i>S. riobrave</i>	Hemi-terpene	Prenol	<i>Galleria mellonella</i> (Lepidoptera)	[13*]

H.: *Heterorhabditis*; S.: *Steinernema*; O.: *Oscheius*. Ref.:reference. ND: Non determined, the authors used synthetic compounds known to be released by insects.

Figure 1



Chemically driven foraging decisions in Entomopathogenic Nematodes (EPNs). Arrows represent possible EPN choices. The wider side of the triangles indicate EPN preferences. Yellow: Carbon dioxide (CO₂), Green/green spheres: Healthy plant volatiles and exudates, Orange/orange spheres: Herbivore-Induced Plant Volatiles (HIPVs) and exudates, Red: Insect-derived cues. Sp.: species. Interrogation marks indicate unknown differentiation by EPNs. The plant species 2 enhances the herbivore quality as a host (e.g. Lower concentrations of secondary metabolites).

therefore attract EPNs [72]. Orienting towards fungal cues may enhance the infection success of EPNs when fungivorous insects are present. The identity and role of fungal volatiles in EPN foraging is receiving an increased attention and will further contribute to better understand EPN foraging strategies in soil.

EPNs also interact with plant pathogens, such as phytopathogenic nematodes (PPNs). Terpenoid volatiles, known to be attractive for EPNs, also attract PPNs to the root vicinity [33]. The benefit for a plant to emit such terpenoids can therefore be counterbalanced, and even reversed, depending on the presence of PPNs in the environment. Yet, it is generally accepted that, during the infection process, EPNs produce nematicidal and repellent compounds, such as ammonia, indole and stilbene derivatives, that kill or deter PPNs [73–75] and thereafter, may limit the impact of PPNs on the plant and EPN success.

EPNs may compete for resources with other herbivore enemies, including different EPN species, arthropods, parasitoids, entomopathogenic fungi or free-living bacterivorous nematodes [69,76–82]. For example, like EPNs, the predatory mites and *Acrobeloides*-group (free-living bacterivorous nematodes) can also be attracted to

chemical cues from rust mite-infested tulip bulbs [83,84]. However, some synergistic effects on infection rates have also been reported between EPNs and entomopathogenic fungi [85–87].

Finally, EPNs also have a myriad of enemies, such as fungi, bacteria, protozoa and other microarthropods in soil [88,89]. Interestingly, some of these enemies are able to either hijack EPN-attractant signals or to lure EPNs in their vicinity. For instance, the nematophagous fungi *Pochonia clamydosporea* can produce 1-octen-3-ol, which is also produced by plants and attractive to EPNs [28,36,90,91]. These potential risks of EPN chemotaxis should also be taken into account during application for insect pest biological control.

The soil matrix as modulator of EPN response

The soil is a complex matrix, whose physical, biological, and chemical properties can considerably influence chemical emission, stability, diffusion, and degradation. For instance, soil moisture, pH, and texture can influence the root HIPV profiles and diffusion [92,93]. Soil microorganisms use plant volatiles as source of carbon, and therefore modulate their abundance and dispersion [94]. Root architecture also influences EPN foraging, with higher root density being negatively correlated with

EPN performance [95]. Root colonized with microbes can alter HIPV emissions, and thereafter, altered EPN attraction [96*]. Therefore, the soil characteristics can considerably modulate EPN signal perception and host-seeking behavior. This phenomenon should be carefully considered when identifying molecules involved in EPN host-seeking.

Application in agriculture

Despite the considerable potential of EPNs in pest control, inconsistencies in efficacy have impaired the development of EPN-based pest management programs [2*,59]. As EPN efficacy largely relies on host-finding and infectivity, exploiting infochemical pathways shaping their foraging behavior may allow the tailoring of powerful strategies to control herbivore pests in agriculture. Several avenues, based on EPN chemical ecology, have been proposed. First, crops could be selected or genetically modified to constitutively emit attractive HIPVs [97]. Yet, this approach requires a thorough investigation of pleiotropic effects. For instance, and despite providing a better protection against root herbivores, transforming maize plants to constitutively release (*E*)- β -caryophyllene compromises plant development, apparent to leaf herbivores, and yield [98]. Furthermore, a constitutive release of EPN attractant may disturb EPN host location. A second approach yielding promising results is the release of EPN-infected cadavers in the field. The use of cadavers confers several advantages such as enhanced EPN protection against unfavorable environmental conditions [99], better dispersal and virulence [100,101], attraction of herbivores [12**,13*], and induction of plant defenses [102*,103]. The effect of EPN-infected cadavers on plants remains to be further investigated to assess possible fitness costs on the plants, as the volatiles or chemicals released from cadavers may induce unnecessary and costly plant defenses. Third, encapsulating EPNs in a shell covered with herbivore attractants and feeding stimulants successfully increased herbivore control in the field [104*,105]. Fourth, EPN selective breeding can increase EPN responsiveness to specific cues [62]. Despite minor trade-offs between responsiveness and infectiveness, selected EPN strains were more effective than original strains in controlling herbivore pests in the field [62]. Finally, EPN previous exposure to insect cues or EPN pheromone increases their host-finding and infectivity [66*,67,68]. These studies provide promising strategies to develop potent biocontrol strategies.

Conclusion

The effort of the research community in characterizing the cues involved in EPN host-seeking has resulted in considerable progress in the field and has set solid foundations for future research. The identification of infochemicals shaping EPN foraging behavior is in its young

age but already demonstrated the large variability of response among and within EPN strains. We recommend a thorough and concerted effort in standardizing and reporting experimental conditions. For example, some factors such as EPN origin, age, or previous experience (rearing conditions) should be reported in all studies. Such endeavor will not only allow the identification of further key infochemicals for EPN foraging but also of modulators of EPN response. Possible modulators highlighted in this review include hierarchical orders of signal integration, EPN specialization degree, selective pressure, age, and experience. Understanding the chemical ecology of entomopathogenic nematodes is pivotal to develop powerful, sustainable, strategies to control insect herbivores in agriculture.

Author contributions

X.Z. and CAM.R. wrote the first draft, reviewed, and edited the manuscript. L.L. and L.K. edited and reviewed the manuscript.

Conflict of interest statement

Nothing declared.

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