Pharmacophagy in Insects: Ecological and Evolutionary Perspectives on the Non-Nutritional Use of Plant Specialized Metabolites

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Abstract

Herbivorous insects can interact with plants in ways that go beyond nutrition, with plant specialized (secondary) metabolites (PSMs) mediating complex non-nutritional relationships. While PSMs often function as anti-herbivore defenses, many insects have evolved strategies to counteract and even exploit these compounds, using them for purposes such as their own defense against antagonists, enhanced mating success, or self-medication. This review explores pharmacophagy, where insects actively seek and acquire specific PSMs from both food and non-food plants for benefits unrelated to nutrition, across different insect orders such as Coleoptera, Orthoptera, Hymenoptera, Lepidoptera, Diptera and Neuroptera. Key examples include the acquisition of cucurbitacins by *Diabrotica* spp., neo-clerodane diterpenoids by *Athalia rosae*, and pyrrolizidine alkaloids by butterflies of the Danaini tribe, each demonstrating unique adaptive uses of non-nutritional plant chemicals. We discuss the intra- and transgenerational transfer of pharmacophagously acquired PSMs among conspecifics and the methods for identifying and testing pharmacophagy, emphasizing the importance of interdisciplinary approaches that combine field observations, behavioral studies, and chemical analyses. The evolutionary pathways leading to pharmacophagy are considered, highlighting selective pressures such as predation, parasitism, and sexual selection. We also address the costs associated with pharmacophagy, including energetic demands and potential toxicity. Extending the discussion to non-insect taxa suggests that pharmacophagy may be a broader ecological phenomenon. By establishing a comprehensive framework for understanding pharmacophagy, we aim to stimulate further research into this intriguing aspect of plant-insect interactions and highlight its potential applications in pest management, conservation, and human health.

Keywords

Pharmacophagy, plant secondary metabolites, chemical defense, non-nutritional exploitation, insect-plant interactions, sequestration, chemical ecology

Manuscript text

Plant insect interactions: the non-nutritional dimension

Plant-insect interactions are multifaceted, with plant specialized (secondary) metabolites (PSMs) playing a critical role in mediating these interactions. Plants produce a wide array of PSMs (Mason & Singer, 2015) that primarily serve as defenses against various abiotic and biotic harms, including insect herbivory. To counteract these defenses, herbivorous insects have evolved several strategies, such as avoidance, enzymatic degradation, excretion, or a reliance on specific microbiota (Genta *et al.*, 2006; Shukla & Beran, 2020; Coolen *et al.*, 2022; Jeckel *et al.*, 2022). When they are able to overcome plant defenses, herbivorous insects can use plants as source of nutrients, while an uptake of PSMs is a byproduct of feeding, often followed by detoxification in some way. However, in several cases, insects even concentrate these PSMs directly, or after some modification, in certain body parts and sequester them for purposes such as, for example, defense against own predators. Over the past decades, various studies have demonstrated that potent PSMs are sequestered by a wide variety of insects (Opitz & Müller, 2009; Beran & Petschenka, 2022). This ability has independently evolved across major herbivorous insect lineages and encompasses the uptake of diverse classes of PSMs.

Interestingly, some insects have been found to explore plants independently of nutrient acquisition, focusing exclusively on obtaining particular PSMs. For example, certain insects rely on specific PSMs and acquire them through specialized behaviors that extend beyond normal feeding. These sequestered compounds can significantly influence insect fitness, providing benefits, for example, in terms of defense and/or reproduction. When insects actively search for specific PSMs, take them up, and use them for purposes other than their metabolism or simple recognition of food plants, this behavior is called pharmacophagy

(Boppré, 1984) (from the Greek ‘pharmakon’ – drug and ‘phagein’ – feeding). Earlier studies have extensively examined specific aspects of PSM utilization, including roles in chemical defense, self-medication, and pheromone synthesis (Opitz & Müller, 2009; Nishida, 2014; Erb & Robert, 2016; Stökl & Steiger, 2017; De Pasqual *et al.*, 2021; Erler *et al.*, 2024). Yet, relatively few studies have differentiated whether these metabolites are obtained from food versus non-food plants, or whether insects seek out these chemicals independently of nutritional needs. Note, however, that insects may not always be specifically attracted to the PSM independently of the food plant, though they may still utilize the PSM when it is present. This review explores representative examples of pharmacophagy (Table 1), highlighting key features along with associated benefits and costs. We also discuss methods for identifying and testing pharmacophagy, along with its evolution. Our goal is to establish a framework for understanding how insects explore plants for non-nutritive purposes and to identify key areas for further research. Additionally, we extend the discussion to other animal taxa to demonstrate the broader relevance of pharmacophagy.

Examples of pharmacophagy

In many Coleoptera and Orthoptera species, larvae and adults possess chewing-biting mandibles and may incidentally ingest PSMs from plants while feeding. In contrast, some PSMs may be selectively taken up for pharmacophagous purposes. For example, pharmacophagy is well documented in rootworm beetles (*Diabrotica* spp., Coleoptera: Chrysomelidae), e.g. *Diabrotica undecimpunctata, Diabrotica virgifera,* that sequester cucurbitacins, highly bitter-tasting triterpenoids, from plants of the Cucurbitaceae family, such as *Cucurbita pepo* and *Cucumis sativus* (Gillespie *et al.*, 2003, 2004; Eben, 2022). Adult rootworms, even those that do not feed on cucurbits during their larval stages, actively seek out cucurbitacin-containing plants to acquire these PSMs. Rootworms that have consumed cucurbitacins experience reduced predation, as the compounds make them unpalatable to predators, such as the Chinese praying mantid (Ferguson & Metcalf, 1985; Shapiro & Mauck, 2018; but see also Gould & Massey, 1984).

In the African bushhopper, *Phymateus leprosus* (Orthoptera: Pyrgomorphidae), both juvenile and adult individuals are attracted to and ingest PSMs such as cardiac glycosides and their aglycones from different plant species, including *Asclepias* species (Seibt *et al.*, 2000). The bushhoppers incorporate these chemicals into their secretions. Seibt et al. demonstrated that the insects preferentially fed on filter papers soaked with extracts containing these cardiac glycosides and aglycones, showing a clear attraction to and consumption of these substances.

Pyrolizidine alkaloids (PAs) are sought PSMs by a wide range of insect species for defensive and reproductive purposes. Both nymphs and adults of the grasshopper *Zonocerus elegans* (Orthoptera: Pyrgomorphidae) are strongly attracted to and consume PAs, also from non-food sources (Boppré *et al.*, 1984). The grasshoppers were observed walking upwind towards PA sources and ingesting the compounds, showing that they can detect and seek out these chemicals from the distance. Notably, these tests were conducted in a resident population of *Zonocerus*, indicating that the PAs effectively lured the insects away from their food plants. The strong stimulatory effect of PAs on *Z. elegans* was further demonstrated by the fact that the insects ingested PAs from the ground, which is unusual for this species, as they typically feed on the tips of plants (Boppré *et al.*, 1984).

In several other holometabolous insects, such as species belonging to the Hymenoptera, Diptera or Lepidoptera, adults usually have reduced mouthparts, allowing them to take up only liquid food. Nevertheless, adults of various insect orders engage in pharmacophagy. For example, adults of the turnip sawfly, *Athalia rosae* (Hymenoptera: Tenthredinidae), feed on nectar of Apiaceae plants. However, they also were found to visit non-food plants of the Lamiaceae, such as *Ajuga reptans* or *Clerodendron trichotomum*, where they “lick” or “nibble” on the leaves without any visible damage to the plant (Kawai *et al.*, 1998; Amano *et al.*, 1999; Paul & Müller, 2021; Singh *et al.*, 2022) (Figure 1). In that way, the adults acquire neo-clerodane diterpenoids ("clerodanoids") from the plants, which they store after slight modification in their body and on the body surface (Brueggemann *et al.*, 2023). These compounds are described to be extremely bitter-tasting (Nishida & Fukami, 1990). Clerodanoids applied on filter paper likewise evoke a strong attraction to the adults (Nishida *et al.*, 1989; Opitz *et al.*, 2012). Insects that have gained clerodanoids are better defended against predators such as preying mantids than insects without access to clerodanoids (Singh *et al.*, 2022). Moreover, clerodanoid-containing adults are more successful in mating — particularly females (Amano *et al.*, 1999) —and engage in more social interactions (Singh *et al.*, 2024a) than those without these compounds.

One classical example of pharmacophagy is found in butterflies of the Danaini tribe (Lepidoptera: Nymphalidae) (Lawson *et al.*, 2021; Boppré & Monzón, 2023). Adults of some Danaini species exhibit the peculiar behavior of seeking out and ingesting PAs from non-nutritional sources such as withered or damaged plants, particularly from the plant families Asteraceae, Apocynaceae, or Boraginaceae, such as species of *Eupatorium* and *Heliotropium*. To take up the compounds, they apply a fluid capable of dissolving PAs with their proboscides and then take up the fluid again. Alternatively, they can scratch fresh leaves and then take up sap exuding from these wounds (Boppré, 1984). Adult butterflies do not consume these chemicals as food; instead, they use them primarily for defense against predators (Nishida, 2002). In the adults, PA acquisition is mostly male-biased, as they use the PAs as precursors for pheromone production and transfer PAs to females as a nuptial gift (see below). Numerous other butterfly species from the Ithomiini tribe, as well as moths from the Arctiini tribe, also exhibit pharmacophagy by actively seeking and consuming pyrrolizidine alkaloids (PAs) from non-nutritive plants as adults (Boppré, 1984; Nishida, 2002). For example, Ithomiini butterflies obtain these alkaloids from decomposing foliage or flowers, primarily from plants in the Boraginaceae and Asteraceae. The PAs protect the butterflies from predators such as spiders (Brown, 1984) and their derivatives have a sexual function as male pheromones (Schulz *et al.*, 2004) (see below, *Intra- and transgenerational transfer of pharmacophagously acquired PSMs among conspecifics*).

Sex-specific pharmacophagy is also known from the melon fly, *Bactrocera cucurbitae* (Diptera: Tephritidae), where male melon flies are attracted to and consume raspberry ketone from different plant species. This PSM, once ingested, is stored in the flies' rectal glands and utilized as sex pheromone to attract mates (Shelly, 2010). Furthermore, raspberry ketone and other pheromone compounds serve a defensive function against predators such as the Asian house gecko (Tan, 2000). When houseflies were treated with synthetic raspberry ketone and offered to geckos, the geckos exhibited a reduced tendency to consume these flies over time. In some other fruit fly species, such as *Bactrocera dorsalis*, *Bactrocera carambolae*, and *Bactrocera correcta*, pharmacophagy of methyl eugenol is well-studied (Wee *et al.*, 2007; Shelly, 2010; Tan & Nishida, 2012). The males of these fruit fly species are attracted to and consume methyl eugenol, which is found in various plants, including species from the Myrtaceae and Lauraceae. Once ingested, methyl eugenol is metabolized and stored in the rectal glands of the flies as a sex pheromone. Methyl eugenol-fed males release pheromones during courtship that not only attract females but also contribute to aggregation behavior, further amplifying the benefits of this pharmacophagy (Shelly, 2010).

Research on *Grammia incorrupta* (previously referred to as *Grammia geneura*) (Lepidoptera: Erebidae) highlights an example of pharmacophagy, where caterpillars selectively consume toxic plants rich in PAs for self-medication, i.e. defense against parasitoids such as tachinid flies or wasps (Singer *et al.*, 2004, 2009). Despite the lower nutritional value of PA-containing plants like *Senecio longilobus*, caterpillars prioritize these over more nutritious food plants, reflecting an evolutionary trade-off between growth and survival. Parasitized caterpillars increase their intake of PAs, which are toxic to developing parasitoids, improving survival against parasitism, but reducing also their own growth efficiency. While parasitized caterpillars benefit from PA ingestion, unparasitized individuals experience decreased survival, illustrating the context-dependent nature of this adaptive change in feeding preferences (Singer *et al.*, 2009). Moreover, pharmacophagous behavior seems to be highly dynamic in *G. incorrupta*. Individuals with early-stage wasp parasitoids enhance feeding on plants containing antioxidants, while fly-parasitized caterpillars engage more in feeding of iridoid glycoside-containing plants. PA intake is mostly found in the later time phase of infection (Smilanich *et al.*, 2011). These findings underscore the complexity of pharmacophagy, where non-nutritional PSMs are crucial for survival under ecological pressures.

Self-medication is also reported from *Drosophila melanogaster* (Diptera: Drosophilidae). Larvae that are infected by parasitoids seek out food sources containing ethanol, which can be released from rotting fruit. Presence of ethanol reduces oviposition by endoparasitic wasps of the generalist *Leptopilina boulardi* and larvae of these wasps show an increased death in fruit fly larvae that consumed ethanol (Milan *et al.*, 2012). Since *Drosophila* feed on fungi developing on rotting fruit, they have evolved a high resistance towards fermentation products, which may turn them highly suited to explore ethanol for self-medication.

In some cases, the target of medication is rather the group or colony. For instance, wood ants (*Formica paralugubris*) frequently incorporate large amounts of solidified conifer resin into their nests (Castella *et al.*, 2008). Laboratory experiments have demonstrated that this resin inhibits the growth of bacteria and fungi under conditions simulating their natural environment. The ants display a clear preference for resin over other common building materials like twigs and stones. This preference varies seasonally, being more pronounced in spring compared to summer, while in autumn the ants collect both twigs and resin at similar rates. In laboratory conditions, the collection rate of resin versus stones is not influenced by infection with the entomopathogenic fungus *Metarhizium anisopliae*, suggesting that resin collection serves a prophylactic rather than a therapeutic function (Castella *et al.*, 2008).

Honey bees (*Apis mellifera*; Hymenoptera: Apidae) also integrate plant-produced resins into their nest structure, which helps lower the chronic elevation of immune responses of individual bees. When honey bee colonies are exposed to the fungal parasite *Ascophaera apis*, they intensify their resin foraging activities. Furthermore, colonies that are experimentally provided with additional resin show reduced levels of fungal infection (Simone-Finstrom & Spivak, 2012). Apart from resin, honey bees collect various plant-derived compounds from sources such as nectar, pollen, and propolis, which contribute to colony health by preventing infections. PSMs in these foraged materials, such as phenolics and flavonoids from pollen, are instrumental in boosting the bees' immune systems and protecting them from pathogens. Honeybees also use antimicrobial compounds found in propolis for nest sanitation and individual immunity (Erler & Moritz, 2016).

Male orchid bees belonging to the tribe euglossini (Hymenoptera: Apidae) are highly attracted to fragrances of orchids (Dressler, 1982; Cameron, 2004). The bees collect these fragrances, store them in pouches in their hind legs and expose them during courtship display (Zimmermann *et al.*, 2006). The odors attract both males and females, forming leks, and seem to exclusively attract individuals within species, acting thus as pheromone analogues, as shown in the species *Eulaema bombiformis* (Zimmermann *et al.*, 2006). Quite complex mixtures of fragrances can be collected by some euglossini, with up to 105 different compounds, mostly essential oils, found in the fragrance in *Euglossa tridentata* (Eltz *et al.*, 1999). Thus, this peculiar collection behavior is discussed to act as “aroma therapy”, potentially increasing the longevity of the bees.

Finally, also predatory insects have been found to be pharmacophagous on plants. Green lacewings (*Chrysopa* spp., Neuroptera: Chrysopidae) usually feed on aphids and other small arthropods. Males of *Chrysopa oculata* lacewings are hypothesized to obtain the aphid pheromone nepetalactol from aphids, while other *Chrysopa* species are reported to obtain the monoterpenoid neomatatabiol by feeding on plants, such as *Actinidia polygama* (silver vine) (Aldrich *et al.*, 2016; Aldrich & Zhang, 2016). These irioid precursors are sequestered and converted into the lacewing pheromone iridodial, which males use to attract females. When kept in the laboratory without access to such food sources, males of *C. oculata* could not produce iridodial on their own (Aldrich *et al.*, 2016), highlighting that they need another food source for reproduction. This behavior showcases the significance of pharmacophagy also in predatory insects.

Intra- and transgenerational transfer of pharmacophagously acquired PSMs among conspecifics

PSMs that are acquired pharmacophagously can also be transferred within the same generation to conspecifics and even to members of the next generation. Some male butterflies of the Danaini tribe use PAs as precursors for their courtship pheromone danaidone, and transfer PAs to females during mating (Dussourd *et al.*, 1989). By selecting males with high pheromone amounts, females gain fitness benefits, since they get also more PAs with their nuptial gifts, which can provide protection against predators. By incorporating PAs into their eggs, they presumably also provide protection to their offspring against parasites and predators (Dussourd *et al.*, 1989). In the moth *Utetheisa ornatrix* (Arctiidae), the eggs are endowed with PAs from both parents and these PSMs serve as protection against predators and parasitoids (Eisner *et al.*, 2000; Bezzerides *et al.*, 2004). Likewise, cucurbitacin consumption in rootworms has been linked to reproductive benefits, as the compounds are passed on to eggs, providing protection to offspring (Tallamy *et al.*, 2000; Shapiro & Mauck, 2018). Indeed, eggs and larvae from parents that had sequestered cucurbitacin-rich diet survived exposure to the fungus *Metarhizium anisopliae*, indicating thus a clear antibiotic benefit (Tallamy *et al.*, 1999). In contrast, when testing the defense of eggs of adults that had fed on cucurbitacin C-containing vs. cucurbitacin C-lacking cucumber, the predation rate by four arthropod predators did not differ significantly (Brusti & Barbercheck, 1992). However, eggs from adults that had fed on cucurbitacin-containing diet had a significantly faster development and larvae hatched faster under different moisture conditions than eggs from adults fed on cucurbitacin-lacking cucumber (Brusti & Barbercheck, 1992). Thus, PSMs acquired pharmacophagously may also provide important ecological functions with regard to abiotic challenges.

PSMs acquired from plants may also be “stolen” by conspecifics. For example, adult sawflies of the species *A. rosae* can obtain clerodanoids from conspecifics via agonistic interactions, such as “nibbling”, or licking, on the body surface (Figure 1)(Paul *et al.*, 2021; Singh *et al.*, 2022). The concentrations in such individuals are usually lower than in the ones that took up clerodanoids directly from the plants (Singh *et al.*, 2022, 2024a), but they still can provide protection against predators and enhance mating success (Singh *et al.*, 2022). However, fighting over these defense chemicals can also disrupt the mating behavior (Paul & Müller, 2021). Sawflies without direct access to clerodanoids also benefit from reduced predation when in groups with clerodanoid-defended individuals (Singh *et al.*, 2022). Experiments with sawflies in different group composition revealed that groups, in which all or some members had clerodanoids, exhibited more frequent social interactions compared to those without clerodanoid access (Figure 1)(Singh *et al.*, 2024a). However, this access also has costs, as adults with clerodanoids paired with individuals lacking these compounds experienced a shortened lifespan, likely due to the increased social and agonistic interactions. More research is needed to study consequences of pharmacophagy on such social interactions and on shaping of the individual social niches (Kaiser *et al.*, 2024; Singh *et al.*, 2024b).

Identifying and testing pharmacophagy

Field observations and behavioral studies on insects are essential for identifying non-nutritional interactions in natural settings. Observations in the wild typically focus on feeding, egg-laying, or nectar gathering, particularly among adult insects. However, when insects rest on plants or dried plant material without feeding, they may be misinterpreted as idle, when in fact they could be gathering crucial non-nutritional chemicals. For instance, *A. rosae* adults have been reported to congregate on plant species of the Lamiaceae (Nishida *et al.*, 1989; Amano *et al.*, 1999), which are not food plants for the larvae and unsuitable for oviposition. Such observations, also made by a previous member of our group in a botanical garden, who found many *A. rosae* hovering over and sitting on *Ajuga reptans* plants (Opitz, personal observation), led to further investigations of this peculiar behavior. Clerodanoids, occurring in *A. reptans* and being taken up by *A. rosae* (see above), or cucurbitanics, occurring in cucumber and attracting *Diabrotica* spp., are known to be highly bitter tasting also for human (Nishida & Fukami, 1990; Brusti & Barbercheck, 1992). Thus, researchers assumed that insects may use these compounds for defensive purposes. If individuals of insect species that typically feed on other plants are observed visiting plants known for active PSMs—such as those with bitter-tasting or antimicrobial properties— such instances could be studied in more detail, as they may suggest pharmacophagy.

To conduct systematic field studies, researchers should note any interactions not directly related to feeding, egg-laying, or shelter, especially on non-host plants. Extended observations can capture repeated, unusual behaviors (e.g., sitting on specific plants without feeding) and track insect movements, contact duration, and revisitation patterns with specific plants. Citizen science initiatives and targeted field surveys can help capture instances of pharmacophagy in diverse locations and understudied habitats. For example, in a garden in Maryland, monarch butterflies were observed gathering PAs from withered *Eupatorium serotinum* plants by probing damaged parts with their proboscides (Lawson *et al.*, 2021). Thus, raising awareness and promoting citizen science could help document similar behaviors across diverse locations, providing insights into potentially pharmacophagous behavior.

To experimentally test pharmacophagy, key predictions should be addressed: (i) insects are attracted to and take up the chemicals, (ii) these chemicals confer a specific functional benefit, and (iii) the chemicals are generally obtained from non-food plants, though they may occasionally come from food plants as well. For this, chemical analysis and metabolite profiling of plant and insect samples collected after apparent interactions can provide further insights. Analytical platforms such as GC-MS or LC-MS can be used to analyze plant and insect samples for the presence of the same PSMs. By comparing metabolite profiles of insects exposed to specific plants with those of controls that were not exposed, we can test for the uptake of PSMs. However, in several insect species, the plant metabolites are further metabolized upon uptake, with minor or larger changes to the core structure, as found, for example, for clerodanoids in *A. rosae* (Brueggemann et al. 2023). This needs to be considered when comparing metabolic data of plant and insect samples. Here, markers or isotopic tracers can help to test for uptake and potential modification of PSMs. Labelling PSMs with markers or isotopes can also allow us to track these chemicals' movement within insect bodies, confirming their integration into tissues or glands for potential use in defense or reproduction. Imaging techniques, such as MALDI-imaging, can be used to localize the areas in an insect body, where sequestered compounds are stored (as in Abdalsamee *et al.*, 2014).

Furthermore, choice and preference bioassays in the laboratory provide a controlled environment for testing attraction to and uptake of specific PSMs. By offering insects a choice between different plant material, containing or lacking the PSMs in question, their attraction, feeding behavior and effects can be observed, as, for example, performed with rootworms and cucurbitacin (Brusti & Barbercheck, 1992) . In that way, we can assess preferences for certain PSMs and score interaction frequencies, further validating field observations. To confirm the role of specific PSMs, they should be purified or synthesized and preference tests be repeated with these compounds being applied on plant material, filter paper, artificial diet or other material that the insects would accept for feeding. Purified or synthetic compounds offered in that way could also be used to monitor changes in insect behavior, physiology, or pheromone production, comparing treated groups with controls to assess specific functional benefits. In such bioassays, also efficiencies of compounds against various predators, parasitoids or pathogens can be tested.

Finally, phylogenetic and evolutionary comparisons can reveal patterns of convergent evolution of pharmacophagy (Zaspel *et al.*, 2014). The oscillation hypothesis proposes that derived herbivore species include plant species of several families for a certain period of time (Nylin & Janz, 2009). In the genus *Athalia*, the use by adults of clerodanoids from Lamiales may point to an ancient association with this plant order. In fact, adults of several *Athalia* species were found to be stimulated to feed on filter paper treated with clerodendrin B, although the larvae of several of those species use clerodanoid-lacking plants as food plants (Opitz *et al.*, 2012). Likewise, a convergent evolution of cucurbitacin feeding has been reported from rootworm taxa that are spatially separated. In line with the ancestral host hypothesis, a common ancestor is predicted that fed solely on cucurbits, while the majority of rootworm species have undergone host plant shifts, but are all still pharmacophagous on cucurbitanics (Gillespie *et al.*, 2003). By comparing the occurrence of pharmacophagy across species that share similar ecological or evolutionary backgrounds, we can assess patterns and possible convergence.

Evolution of pharmacophagy

Non-nutritional uptake of PSMs by insects may evolve through a combination of selective pressures that favor survival, reproduction, and niche expansion. For example, there could be selection for defense against predation and parasitism, and this may lead to pharmacophagous behavior, as insects capable of acquiring PSMs from non-food plants often gain a direct survival advantage. For instance, PAs obtained from various non-host plants provide effective chemical defense in multiple insect taxa, such as Ithomiine butterflies (Brown, 1984) and *Grammia incorrupta* caterpillars (Singer *et al.*, 2004). This defensive strategy may represent an evolutionary shift, where non-food plants become crucial resources for survival rather than nourishment. Moreover, studies suggest that self-medication may be widespread among insects (Erler *et al.*, 2024), potentially acting as a selective force behind pharmacophagous behavior. Insects affected by parasitism or disease may develop preferences for non-food plants containing PSMs with medicinal properties. Consequently, behaviors that enhance health through non-nutritional chemical intake can evolve as stable adaptive traits in populations under high parasite or pathogen pressures.

Behavioral shifts and adaptive flexibility may be a prerequisite for shifts to other host plant sources to evolve. Behavioral plasticity allows insects to adapt existing behaviors to new functions, such as sourcing PSMs for purposes other than feeding. Initial contact with non-food plants may be incidental or linked to oviposition or shelter-seeking behaviors. The evolution of these behaviors likely involves exaptation, where traits originally evolved for herbivory are repurposed for non-nutritional uses. This may even lead to exploitation of conspecifics such as in *A. rosae*, where adults exhibit behaviors such as nibbling on conspecifics to acquire defensive compounds from individuals that had acquired these compounds from plants (Paul *et al.*, 2021; Singh *et al.*, 2022, 2024a).

Sexual selection and reproductive benefits associated with the uptake of the PSMs are another strong selective force, particularly if these compounds enhance mating success or offspring fitness, as seen in the examples above of Danaini butterflies (Boppré, 1986; Wink, 2019) or fruit flies (Tallamy *et al.*, 2000; Shapiro & Mauck, 2018). The usage of non-nutritional plant chemicals from non-food plants may have arisen from ancestral host plant use and subsequent host plant shifts. If these chemicals confer fitness benefits, such associations are likely to persist. For example, the close relationship between butterflies of the Danaini tribe and PAs likely originated from the exploitation of PA-containing plants as ancestral hosts. Despite shifts from PA-host plants to non-PA hosts, adult Danaini butterflies have maintained their pharmacophagous behavior, suggesting that certain PAs continue to play a crucial role in their reproductive strategy (Nishida, 2002). A similar ancient association with clerodanoids is described above for the genus *Athalia* (Opitz *et al.*, 2012) and for cucurbitacins in rootworm taxa (Gillespie *et al.*, 2003).

There can also be co-evolution with and niche expansion to new PSMs. Plants evolve novel PSMs, towards which herbivores evolve adaptations, driving a co-evolutionary arms race between plants and insects (Ehrlich & Raven, 1964; Agrawal *et al.*, 2009), which led to their co-diversification. This co-diversification may also foster the evolution of pharmacophagy. Moreover, accessing PSMs from non-food sources allows insects to explore new ecological niches, reducing competition and promoting adaptive niche expansion and diversification. We may also expect such niche shifts to occur more readily in species that are more mobile and can sample multiple plants during their lifetime or at least during adulthood, such as lepidopteran flying adults. In contrast, species like smaller aphids may not be mobile enough to visit a non-food plant to collect new PSMs, although this may depend on the species-characteristic dispersal ability.

Finally, genetic adaptation and physiological changes are important pre-requisites to manifest the genetic basis for detoxification, sequestration, or metabolizing plant-derived chemicals and be able to detect them (Heidel-Fischer & Vogel, 2015). Over time, selective pressures may favor individuals with genetic mutations that confer tolerance or detoxification capabilities, enabling them to exploit non-food plants for defense or reproductive benefits. Also, taste receptors may need modifications to be stimulated by the PSMs causing pharmacophagous behavior. The loose receptor hypothesis postulates that some gustatory receptors have only loose binding properties and thus allow for novel, potentially deleterious compounds to trigger feeding (Tallamy *et al.*, 1999). This may thus be a coincidence rather than adaptive in the beginning, but further selection or modification of receptors may occur afterwards, if feeding a specific PSM may have a benefit. This path is discussed to have, for example, supported pharmacophagy of cucurbitacins in rootworm beetles (Tallamy *et al.*, 1999). Further research into the genetic, physiological and ecological mechanisms could illuminate the broader evolutionary framework underlying pharmacophagy and its role in shaping insect biodiversity.

Costs of pharmacophagy

The uptake of PSMs may come be costly in some scenarios. For example, locating and acquiring these compounds can be both energetically demanding and time-consuming, increasing exposure to predators during the search for suitable plants. Additionally, metabolizing these chemicals could further strain the individual's energy resources, especially if these chemicals are toxic in high concentrations. For example, growth and survival costs have been found in *G. incorrupta* when feeding on PA-containing plants (Singer et al. 2009). Thus, these compounds are likely only taken up when the immune response is not sufficient. Individuals having acquired PSMs pharmacophagously also showed reduced longevity, even in absence of a predator or parasitoid, for example in *A. rosae*, compared to control individuals that had not taken up these compounds (Zanchi *et al.*, 2021). Finally, competition for these valuable PSMs might trigger intraspecific aggression, as also found in *A. rosae*, where fighting for clerodanoids can interfere with mating (Paul & Müller, 2021).

Non-nutritional exploration of plants in non-insect taxa

Non-insect taxa also engage in non-nutritional interactions with plants, exploring them for benefits beyond food. Indeed, some vertebrates exhibit self-medicative behaviors, seeking specific plants to counteract parasites or treat ailments (De Roode *et al.*, 2013). For example, a Sumatran orangutan was observed using a liana (*Fibraurea tinctoria*) containing furanoditerpenoids and protoberberin alkaloids to treat a wound (Laumer *et al.*, 2024). Moreover, primates such as gorillas and chimpanzees have been observed swallowing whole leaves, which remain undigested as they pass through the digestive system and are later excreted intact, aiding in parasite removal (Huffman, 2003). For instance, chimpanzees consume leaves from *Aspilia* plants, whose trichomes physically attach to intestinal parasites, facilitating their expulsion. Chimpanzees also ingest the bitter pith of *Vernonia amygdalina* to control intestinal nematode infections. African elephants reportedly chew leaves from certain Boraginaceae species to induce labor, a practice also utilized by local human populations for the same purpose (Huffman & Vitazkova, 2007). Sheep infected with nematodes modify their feeding behavior by increasing their preference for diets rich in plant bioactive compounds, likely as a self-medicative response, though this preference may not necessarily reduce parasite loads or impact health markers (Poli *et al.*, 2018). These behaviors suggest a widespread, adaptive strategy where animals use plants for health benefits, far beyond simple nutrition. However, in some instances, it may be plant morphology, rather than plant chemicals, that provides the advantage. Additionally, in cases involving PSMs, it remains unclear whether these compounds act as phagostimulants. Thus, further research is needed to test whether pharmacophagy, in the strict sense (Boppré, 1984), also occurs in non-insect taxa.

Future directions

Research into pharmacophagy among insects offers exciting opportunities to broaden our understanding of insect ecology and evolution. Future studies should prioritize expanding taxonomic and ecological coverage of pharmacophagy, as current evidence largely focuses on a few well-studied taxa and chemical classes, leaving significant gaps in understanding the prevalence and diversity of these interactions. Moreover, while we here primarily focused and discussed pharmacophagy in terrestrial insects, it may occur in aquatic animals too (Putz & Proksch, 2010; Dettner, 2019), which needs to be explored more. A more detailed examination of the physiological and genetic mechanisms that enable pharmacophagy is also essential. Integrated 'omics' approaches combining genomics, transcriptomics, and metabolomics will be instrumental in mapping the fate of PSMs within insect bodies—from uptake and sequestration to potential chemical modifications. Exploring the ecological consequences of pharmacophagy could reveal how these interactions affect community dynamics and plant-insect networks. For instance, by incorporating PSMs, pharmacophagous insects could influence predator-prey interactions, contribute to shaping trophic relationships (Trigo, 2011), and affect overall community resilience, particularly if sequestration of PSMs alters palatability or defensive strategies. Examining whether pharmacophagy affects conspecific and interspecific interactions, such as competition, mate choice, or mutualistic relationships, will provide a deeper understanding of its ecological implications. Moreover, pharmacophagy may influence an animal's microbiota or even be facilitated by it. The role of gut microbiota in modulating the detoxification, sequestration, or bioactivation of ingested plant compounds remains underexplored (but see, e.g. Genta *et al.*, 2006 and Shukla & Beran, 2020 for detoxification); the gut microbiome may facilitate pharmacophagy by metabolizing otherwise toxic PSMs or enhancing their bioactivity.

Finally, there is potential to apply insights from pharmacophagy research to pest management and conservation. Identifying PSMs that act as attractants for insects could support the development of biologically based pest management strategies in agriculture. For example, kairomone traps with cucurbitacins are used to control *Diabrotica* spp. (Arruda-Gatti *et al.*, 2006), which is more environmentally friendly and sustainable than synthetic pesticides. PSMs that attract different species may also be used for biodiversity surveys. Moreover, investigating how pharmacophagous behavior impacts insect survival under environmental challenges, such as pathogens and climate change, could inform conservation strategies for both beneficial and threatened species. Additionally, humans have long utilized PSMs for various purposes, including medicinal uses (Wink, 2010), suggesting a possible relevance of PSMs for human health, e.g., to synthesize antimicrobial or antifungal agents (Reichling, 2010) or as templates for drug development. Collectively, advancing our understanding of pharmacophagy promises to uncover intricate ecological relationships and reveal valuable applications in sustainable pest management, conservation, and even human health, emphasizing the broader relevance of these unique exploration of PSMs.

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Figures

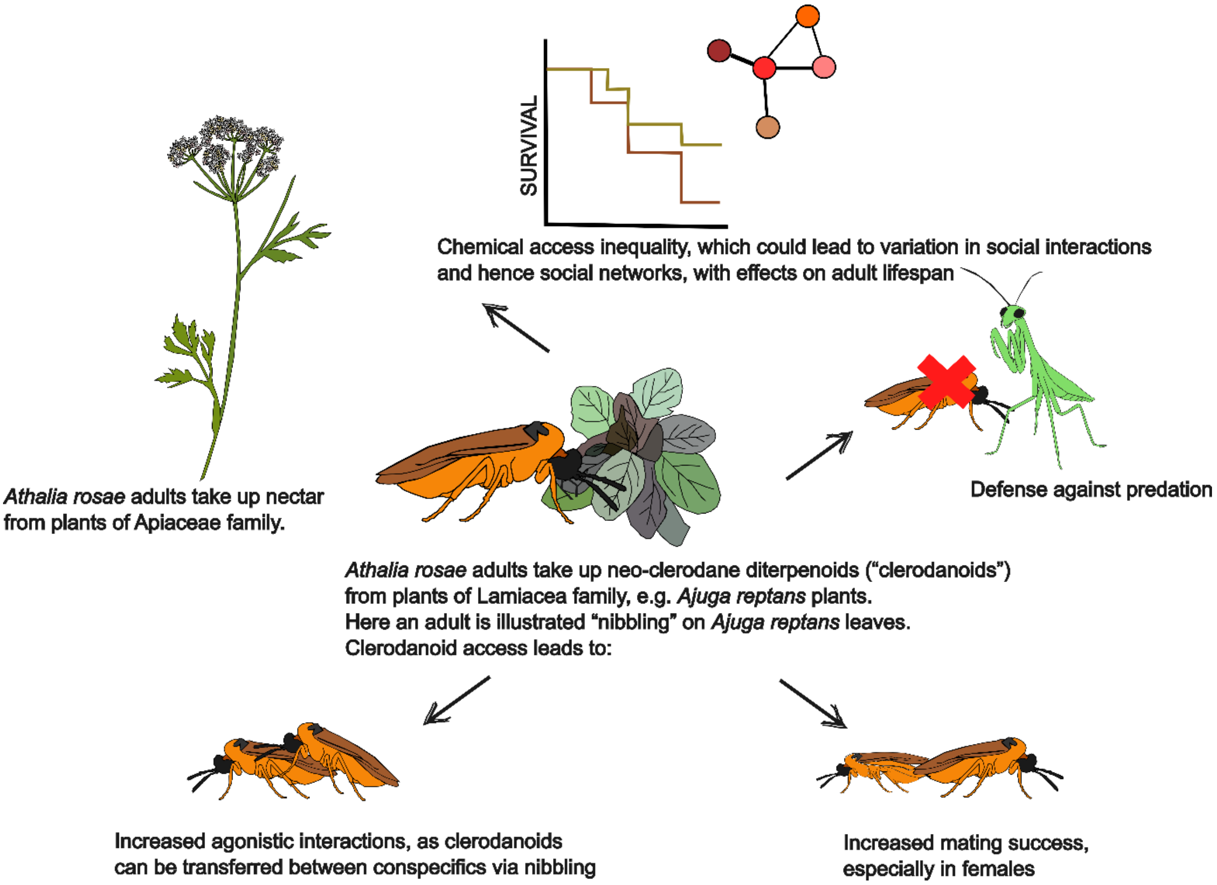

Figure 1. Pharmacophagy in the turnip sawfly (*Athalia rosae*): Acquisition, transfer, and ecological impacts of neo-clerodane diterpenoids ("clerodanoids"). Adults feed on nectar from Apiaceae plants, which provides nutrients but no clerodanoids (top left). Clerodanoids are obtained by "nibbling" on leaves of *Ajuga reptans* plants (Lamiaceae) (center), providing chemical defense and impacting behavior. Clerodanoids defend against predation, e.g. against mantids (top right). Clerodanoids can be transferred between individuals via agonistic nibbling, increasing social interactions and affecting social networks and lifespan (bottom left and top). Access to clerodanoids enhances mating success, especially in females (bottom right). Together, these elements illustrate how pharmacophagy influences predator defense, social dynamics, and mating success in *A. rosae*.

Table

Table 1. Examples of pharmacophagy in various insect taxa, listed in the order they appear in the text. For each example, details are provided on the plant species and compounds utilized, insect feeding types, life stages, and sex, as well as the functional role of the plant compound (e.g., chemical defense, mating success), effects on fitness, any conspecific transfer.

Insect Order	**Insect species**	**Plant species used for pharmacophagy**	**Insect feeding type**	**Insect life-stage, sex**	**Compound being utilized (either without modification or its derivative)**	**Function of compound, i.e. what is the plant compound or its derivative being used for**	**Effect on fitness or fitness proxy**	**Remarks**	**Reference**
Coleoptera	*Diabrotica undecimpunctata*, *Diabrotica virgifera,*other *Diabrotica sp.*	Cucurbitaceae, e.g. *Cucurbita pepo, Cucumis sativus*	biting-chewing	adult, both sexes	cucurbitacins	chemical defense, survival in the presence of entomopathogenic fungi, mating success			(Gillespie *et al.*, 2003, 2004; Eben, 2022)
Orthoptera	*Phymateus leprosus*	*Asclepias* species	biting-chewing c	juvenile & adult	cardiac glycosides and aglycones	potentially chemical-defense		taken from food plant, but PSM independently also taken up	(Seibt *et al.*, 2000)
Orthoptera	*Zonocerus elegans*	*Senecio* (Asteraceae), *Heliotropium,* and *Crotalaria* (Fabaceae) species	biting-chewing	nymphs and adults, both sexes	pyrrolizidine alkaloids (e.g. heliotrine, senecionine and fuchsisenecionine)	potentially chemical defense		aposematic coloration	(Boppré *et al.*, 1984)
Hymenoptera	*Athalia rosae*	Lamiaceae, e.g. *Ajuga reptans* and	nectar feeding as adults	adults, both sexes	neo-clerodane diterpenoids (“clerodanoids”)	defense against predation, impacts on mating success	reduces lifespan when alone or in groups	transferred to conspecifics via “nibbling”	(Amano *et al.*, 1999; Paul *et al.*, 2021; Paul &

		Clerodendron trichotomum					with asymmetric clerodanoid access, possibly due to higher agonistic interactions		Müller, 2021; Zanchi *et al.*, 2021; Singh *et al.*, 2022, 2024a)
Lepidoptera	Danaini species	plant species of Apocynaceae, Asteraceae, Boraginaceae, and Fabaceae	nectar feeding as adults	adults, usually males	pyrrolizidine alkaloids	chemical defense, sex pheromone, reduce or prevent infection			(Boppré, 1986; Lawson *et al.*, 2021; Boppré & Monzón, 2023)
Lepidoptera	Ithomiine species	Asteraceae (Eupatorieae) and Boraginaceae	nectar feeding as adults	adult, nectar-feeders	pyrrolizidine alkaloids (specifically dehydropyrrolizidine, alkaloid monoesters and their n-oxides)	chemical defense, reproduction	increase chances of mating	warning coloration	(Brown, 1984)
Diptera	*Bactrocera cucurbitae*	plants that secrete raspberry ketone as a fruit scent in raspberry or as a floral fragrance in several orchid species, e.g., *Dendrobium annosmum, Bulbophyllum ecornutum and Bu. macranthum*	nectar feeding as adults	adult males	raspberry ketone	chemical defense, courtship and aggregation pheromone			(Tan, 2000)
Diptera	*Bactrocera carambolae*	Reported from 30 plant families,	nectar feeding as adults	adult, males	methyl eugenol	sex-pheromones	reproductive success	taken from food plant	(Wee *et al.*, 2007)

		such as *Ocimum basilicum, Persea americana, Mangifera indica, Melaleuca* spp.							
Lepidoptera	*Grammia incorrupta (Grammia geneura*	*Senecio longlibus*	biting-chewing as larvae	larvae	pyrrolizidine alkaloids	resistance against parasitoids	survival at cost of growth	taken from food plant	(Singer *et al.*, 2004)
Diptera	*Drosophila melanogaster*	rotting fruit	Reduced larval mouthparts with extension and retraction of the mouth hooks	larvae	ethanol	resistance against endoparasitoid			(Milan *et al.*, 2012)
Hymenoptera	*Formica paralugubris*	conifers	biting-chewing as adults	adults	resin	antimicrobial for colony		impact on colony	(Castella *et al.*, 2008)
Hymenoptera	*Apis mellifera*	plant-produced resins	nectar feeding as adults	adults	resin	antifungal for colony		impact on colony	(Simone-Finstrom & Spivak, 2012)
Hymenoptera	*Euglossini*	orchids	nectar feeding as adults	adults, males	terpenoids	territorial display and courtship	enhances longevity		(Eltz *et al.*, 1999; Cameron, 2004; Zimmermann *et al.*, 2006)
Neuroptera	*Chrysopa oculate,* observations also	*Nepeta cataria, Actinidia polygama*	predatory	adults, males	iridoid precursors	sex pheromone synthesis			(Aldrich *et al.*, 2016;

	for other *Chrysopa* species								Aldrich & Zhang, 2016)

* Note that our interpretation of the phenomena as pharmacophagy may differ from the authors' terminology in their study.