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Understanding effects of floral products on bee parasites: Mechanisms, synergism, and ecological complexity

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ABSTRACT

Floral nectar and pollen commonly contain diverse secondary metabolites. While these compounds are classically thought to play a role in plant defense, recent research indicates that they may also reduce disease in pollinators. Given that parasites have been implicated in ongoing bee declines, this discovery has spurred interest in the potential for 'medicinal' floral products to aid in pollinator conservation efforts. We review the evidence for antiparasitic effects of floral products on bee diseases, emphasizing the importance of investigating the mechanism underlying antiparasitic effects, including direct or host-mediated effects. We discuss the high specificity of antiparasitic effects of even very similar compounds, and highlight the need to consider how nonadditive effects of multiple compounds, and the post-ingestion transformation of metabolites, mediate the disease-reducing capacity of floral products. While the bulk of research on antiparasitic effects of floral products on bee parasites has been conducted in the lab, we review evidence for the impact of such effects in the field, and highlight areas for future research at the floral product-bee disease interface. Such research has great potential both to enhance our understanding of the role of parasites in shaping plant-bee interactions, and the role of plants in determining bee-parasite dynamics. This understanding may in turn reveal new avenues for pollinator conservation.

1. Introduction

Plants produce an extraordinary diversity of secondary metabolites thought to primarily serve as signaling molecules and defense against herbivores and pathogens (Moore et al., 2014; Schoonhoven et al., 2005). The distribution of these compounds across tissues is variable (Kaplan et al., 2008), but defense compounds found in vegetative tissues also frequently occur in nectar and pollen (Palmer-Young et al., 2019; Stevenson, 2020). For example, grayanotoxin 1 is a defense chemical in the vegetative tissues of *Rhododendron simsii* (Scott-Brown et al., 2016), but also occurs in the nectar of other *Rhododendron* species at concentrations that are toxic to western honey bees (*Apis mellifera*) and the mining bee *Andrena scotica* (although not to bumble bees) (Tiedeken et al., 2016). The presence of toxic chemicals in nectar is counter-intuitive, since nectar is a reward for pollinators (Adler, 2000; Irwin et al., 2014; Stevenson et al., 2017). The occurrence of defense compounds in pollen is less surprising, since pollen 1) contains the male gametes, making it a high priority tissue (Rivest and Forrest, 2020), and 2) represents a significant investment of nitrogen, which is frequently a limiting resource for plants. Nevertheless, pollen is the sole source of food for many invertebrates and an attractant for many pollinators; the presence of defense compounds or toxins at high concentrations therefore presents a challenge to pollen-feeding animals (e.g., Arnold et al., 2014; Eckhardt et al., 2014).

Conversely, biologically active compounds in nectar may have benefits for pollination, for example by optimizing specialized pollinator syndromes through selective toxicity (Barlow et al., 2017) or, as in the case of caffeine, increasing pollinator memory for floral traits and thereby increasing visitation to target flowers and nestmate recruitment (Arnold et al., 2021; Couvillon et al., 2015; Thomson et al., 2015; Wright et al., 2013). When these nectar metabolites are biologically active against microorganisms, they may also protect nectar-feeding animals

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from disease (Koch et al., 2017). For example, Manson et al. (2010) reported activity of the alkaloid gelsemine, present in the nectar of *Gelsemium sempervirens* flowers, against the bumble bee-infecting trypanosome *Crithidia bombi* when gelsemine was consumed post-infection. More recently, the metabolite callunene has been reported in the nectar of heather (*Calluna vulgaris*) at concentrations that significantly reduce acquisition of *C. bombi* in live bees fed honey derived from heather, demonstrating an ecologically relevant example of natural 'medicines' for bees (Koch et al., 2019).

Improved understanding of the effects of floral products (i.e., pollen and nectar) on bee parasites has the potential to provide new insight into the ecological significance of secondary metabolites in pollen and nectar. At the same time, this understanding can open new avenues for promoting pollinator health. Given mounting concerns about ongoing bee declines (Potts et al., 2010; Rodger et al., 2021; Vanbergen and Initiative, 2013; Zattara and Aizen, 2021), and the recognition that parasites, in combination with other stressors, may be contributing to these declines (Averill et al., 2021; Cameron et al., 2011; Goulson et al., 2015), there has been a recent surge in interest in the therapeutic and preventive potential of phytochemicals against bee disease. Much of this work has been motivated by an interest in controlling disease in commercial honey bee colonies, and includes many phytochemicals that are unlikely to be encountered by wild-foraging bees, at least not at the concentrations to which they are exposed in experimental studies (e.g., Boncristiani et al., 2021; Flesar et al., 2010; Maistrello et al., 2008). This research has advanced in parallel with growing interest in leveraging the antimicrobial and antifungal capacity of phytochemicals to promote human health by 'natural' means. The latter research agenda has resulted in an explosion of papers on the antimicrobial effects of honey (reviewed in Mărgăoan et al., 2021; Nolan et al., 2019; Samarghandian et al., 2017) and on the utility of phytochemicals in food preservation (reviewed in Bassolé and Juliani, 2012; Gutiérrez-del-Río et al., 2021; Redondo-Blanco et al., 2019). Recognizing that findings from these contexts may not neatly translate to wild pollinator host-parasite systems, we nevertheless believe that efforts to integrate these literatures would generate helpful insights and new avenues for study.

Here, we review the existing literature on the antimicrobial effects of floral products on bee parasites to highlight gaps in our understanding, emphasize the importance of investigating the mechanism(s) underlying antimicrobial effects, and propose fruitful directions for future research. While research clearly demonstrates the importance of diet nutritional content in determining the outcome of parasite infection in bees (e.g., Brown et al., 2000; Conroy et al., 2016; Di Pasquale et al., 2013; Dolezal and Toth, 2018; Jack et al., 2016; Sadd, 2011), we focus here on more strictly 'medicinal' effects – that is, effects not mediated by diet macronutrient content (recognizing that the distinction between nutritional effects and medicinal effects is not always clear-cut). We define medicinal effects broadly to include both the effects of phytochemicals and, for pollen, mechanical effects on parasite infection, transmission and virulence. While we recognize the importance of macroparasites (including ectoparasites, parasitoids, and brood parasites) for pollinator health, we will limit our focus to microparasites. We do this because 1) the mechanisms of antiparasitic effects are likely to differ substantially between micro- and macroparasites, and 2) to date, very little work has focused on the effects of floral products on bee macroparasites [with the exception of *Varroa destructor*, an ectoparasitic mite that is a major pest of the western honey bee and the target of substantial research on the acaricidal effects of phytochemicals (reviewed in Camilo et al., 2017; Singh, 2014)].

Our review first summarizes the breadth of lab-based research conducted to date on the effects of floral products on bee parasites, highlighting the need to study these effects in a wider range of both parasite and host species, and makes the primary distinction between direct chemical and host-mediated effects (Section 2; see Fig. 1). In Section 3,

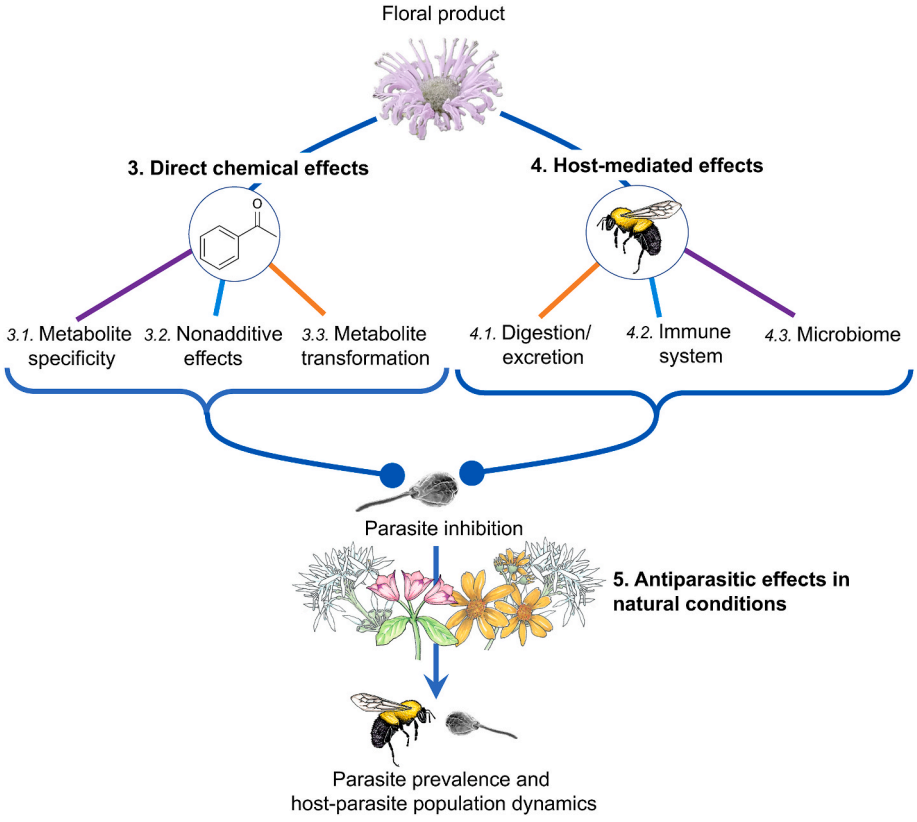

Fig. 1. Floral products may reduce bee disease via multiple mechanisms, including both direct and host-mediated effects; the influence of these effects on population-level parasite prevalence and host-parasite population dynamics will depend on environmental context. Numbers in diagram refer to corresponding sections of the text where topics are discussed.

we discuss direct chemical effects of floral products in detail. We first emphasize the specificity and context dependence of effects of individual metabolites, and caution against making generalizations across families of compounds (Section 3.1). We then discuss the prevalence and significance of nonadditive effects of combinations of floral products (Section 3.2), and the importance of considering post-ingestion transformation of metabolites when translating between *in vitro* and *in vivo* studies (Section 3.3). In Section 4, we turn to host-mediated effects, presenting the evidence for effects of floral products on the antiparasitic roles of host digestion and excretion, immune defense, and the gut microbiome. We discuss experimental approaches to teasing apart the contributions of each of these potential mechanisms. Finally, in Section 5, we consider how antiparasitic effects of floral products might influence parasite dynamics and bee behavior under field conditions. Here, we emphasize the need for further research that evaluates the effects of parasite infection on bee foraging preferences, and considers the effects of environmental variation. We conclude with recommendations for future research directions we believe hold particular promise.

2. The state of the field

The majority of research on antiparasitic effects of floral products has focused on testing the effects of consumption of one to several constituent phytochemicals on infection intensity in experimentally infected bees (Table 1). Other studies have assessed the effect of entire floral products (i.e. intact pollen or nectar) on infection intensity (e.g., Giacomini et al., 2018), or evaluated the effects of phytochemicals on parasite growth *in vitro* (Palmer-Young et al., 2016). Studies have evaluated the antiparasitic activity of >25 metabolites, belonging to >10 classes of compounds, with alkaloids and terpenoids most frequently studied (Table 1). While numerous microparasites are known to infect bees, the vast majority of research has focused on just two: the trypanosomatid *C. bombi* and, to a somewhat lesser extent, microsporidians in the genus *Nosema*. Viruses [e.g., deformed wing virus (DWV); de Miranda and Genersch, 2010], bacteria (e.g. *Paenibacillus larvae*; Ebeling et al., 2016), fungi (e.g. *Ascophaera apis*; Heath, 1982), and neogregarines (e.g. *Apicystis bombi*; Lipa and Triggiani, 1996) are all known disease-causing agents in bees, and deserve greater attention regarding the potential for floral products to reduce infection. Research has similarly focused on a very narrow subset of bees, specifically the western honey bee (*Apis mellifera*) and a few bumble bee species (particularly *Bombus impatiens* and *B. terrestris*). Given the high degree of variability in antiparasitic effects found even among congeneric host species (Fowler et al., 2022), there is a clear need to expand the scope of research to include a wider diversity of bee species. This need is particularly urgent in light of evidence that disease burden is associated with population declines, at least in bumble bees (Averill et al., 2021; Cameron et al., 2011), and interest in using flowering species with demonstrated antiparasitic effects to reduce disease burden in wild bees (Folly et al., 2021). To evaluate the utility of such approaches, we need to know how floral products influence disease in a wide range of bee species, and particularly those of conservation concern.

To date, most studies of the effects of floral products on bee disease have not explicitly investigated the underlying mechanism. Antiparasitic effects of floral products can arise from multiple mechanisms (Fig. 1), and improving our mechanistic understanding of the antiparasitic effects of floral products in specific instances should help make sense of often complicated or inconsistent patterns in inhibitory effects across bee species (and among individuals within species) and parasites. One important mechanistic distinction is between antiparasitic effects that result from metabolites found in or derived from the floral product, which we term direct chemical effects, and those that result from the influence of the floral product on one or more aspects of host biology, which we refer to as host-mediated effects.

3. Direct chemical effects

Direct chemical effects occur when metabolites found in nectar or pollen inhibit parasite growth, viability, or infectivity. The mechanisms underlying direct chemical effects are diverse. For example, many terpenoids, such as thymol, act as membrane disruptors (Bassolé and Juliani, 2012; Chavan and Tupe, 2014; Xu et al., 2008), while bioactivity of the flavonoid kaempferol results from its activity as an inhibitor of DNA gyrase (Collins et al., 2019). The mechanism underlying bioactivity of many other metabolites is unknown (Nolan et al., 2019).

It is relatively straightforward to quantify direct chemical effects using parasites cultured *in vitro*, since such effects do not rely on interaction between floral products and the host. Studies taking this approach have documented direct effects of several phytochemicals found in floral nectar on *C. bombi* (Koch et al., 2019; Palmer-Young et al., 2016, 2017b) and multiple species of pathogenic bacteria associated with the honey bee disease European foulbrood (Wiese et al., 2018). Studies of other parasites would be fruitful, particularly with phytochemicals where effects on parasite infection have already been documented *in vivo*, but the mechanism is unknown. At the same time, as we discuss below, the inhibitory effects of a particular metabolite on a parasite measured *in vitro* may not directly translate into the effect that metabolite will have on parasite infection once consumed by the host. Thus, caution is warranted in extrapolating from *in vitro* studies to *in vivo* contexts.

3.1. Specificity and context dependence in the effects of phytochemicals

Many ecological studies that investigate the phytochemical traits mediating biological interactions between plants and other organisms, such as herbivores or disease, quantify variation at the compound group level (e.g., total alkaloids and total phenolics; Mikulic-Petkovsek et al., 2013). Such approaches are valuable because they can facilitate the rapid assessment of large numbers of biological samples or interactions, without requiring a detailed understanding of the underlying chemical diversity, and can be implemented using simple reagents. For example, total phenolics can be measured by treating an extract with Folin-Ciocalteu reagent (Bärlocher and Graça, 2020) and using colorimetry to assess the formation of blue complexes of phosphomolybdic and phosphotungstic acid (Singleton et al., 1999; Singleton and Rossi, 1965). Similarly, alkaloid levels can be determined using Dragendorff's reagent (Sreevidya and Mehrotra, 2003). The disadvantage of these approaches is that they do not distinguish among thousands of different plant chemical structures that share a common moiety (structural feature) that may have no influence on its biological activity. For example, phenols have just one phenolic group (hydroxylated benzene ring) in common, but otherwise vary tremendously in structure and biological activities (Chowański et al., 2016; Singh et al., 2021). Each broad class of compounds is comprised of multiple sub-groups, which include compounds that have a multitude of functions and biological activities. Consequently, the value of total estimates of compound groups are at best limited, and not a proxy for understanding which plant compounds mediate specific biological effects (e.g., Heil et al., 2002). The specificity of activity within compound groups is apparent from Table 1, and is illustrated by Richardson et al. (2015), who reported on the biological activity of a variety of nectar compounds against the trypanosomatid parasite of bumble bees, *C. bombi*. Nicotine and anabasine, two pyridine alkaloids, significantly reduced *C. bombi* infections in the bumble bee *B. impatiens*, but the purine alkaloid caffeine had no significant effect. Thus, correlating total alkaloids with *C. bombi* inhibition may be uninformative, depending on alkaloid composition.

There are relatively few examples of phytochemical specificity relating directly to bee parasites, but many illustrate specificity against related microorganisms. For example, stilbenes (e.g., resveratrol) are a group of phenolic compounds produced by plants in response to

Table 1
Documented *in vivo* and *in vitro* effects of floral products and secondary metabolites known to occur in floral products on bee microparasites.

Floral product or metabolite	Metabolite type	Source plant(s)	Host species	Parasite					
				Crithidia bombi	*Nosema* sp.	*Lotmaria passim*	Deformed wing virus	Other viruses	Pathogenic bacteria
***In vivo* effects**									
Anabasine	Alkaloid	*Nicotiana glauca*	*B. impatiens*	−[a], −[b], +/−[c]					
Caffeine	Alkaloid	Multiple plant families	*A. mellifera*		−[d]		−[e]	=[f], −[e]	
Caffeine	Alkaloid	Multiple plant families	*B. impatiens*	=[b]					
Caffeine	Alkaloid	Multiple plant families	*B. terrestris*		−[g]				
Gelsemine	Alkaloid	*Gelsemium sempervirens*	*B. impatiens*	−[h]					
Nicotine	Alkaloid	*Nicotiana* spp.	*A. mellifera*		=[i]				
Nicotine	Alkaloid	*Nicotiana* spp.	*B. impatiens*	=/−[j], −[b], +/−[c]					
Nicotine	Alkaloid	*Nicotiana* spp.	*B. terrestris*	−[k]					
Amygdalin	Cyanogenic glycoside	*Prunus* spp.	*B. impatiens*	=[b]					
Amygdalin	Cyanogenic glycoside	*Prunus* spp.	*A. mellifera*		=[l]	=[l]			=[l]
Quercetin	Flavonoid	Widespread	*A. mellifera*					=[f]	
Kaempferol	Flavonoid	Widespread	*A. mellifera*		−[d]				
Rutin	Flavonoid glycoside	Multiple plant families	*B. impatiens*	=[m]					
Gallic acid	Hydroxy-cinnamic acid	Multiple plant families	*A. mellifera*		−[d]				
Gallic acid	Hydroxy-cinnamic acid	Multiple plant families	*B. impatiens*	=[b]					
p-Coumaric acid	Hydroxy-cinnamic acid	Widespread	*A. mellifera*		−[d]			=[f]	
Aucubin	Iridoid glycoside	Multiple Asterids	*B. impatiens*	=[b]					
Catalpol	Iridoid glycoside	Multiple Lamiales families	*B. impatiens*	−[b]					
Biochanin A	Isoflavone	*Trifolium pratense*	*B. terrestris*		=/−[n]				
Callunene	Megastigmane	*Calluna vulgaris*	*B. terrestris*	−[r]					
Triscoumaroyl spermidine	Polyamine	*Helianthus annuus*	*B. impatiens*	=[m]					
Resveratrol	Stilbene	Widespread	*A. mellifera*		=[o]				
Abscisic acid	Terpenoid	Widespread	*A. mellifera*		−[p]				
Carvacrol	Terpenoid	Lamiaceae	*A. mellifera*					=[f]	
Thymol	Terpenoid	Lamiaceae	*A. mellifera*		−[q], −[o]			=[f]	
Thymol	Terpenoid	Lamiaceae	*B. impatiens*	=/−[j], −[b]					
Sunflower-derived honey		*Helianthus annuus*	*A. mellifera*		−[s]				
Sunflower pollen		*Helianthus annuus*	*B. impatiens*	−[m], −[t], −[u], =/−[v], −[w], −[x]					
***In vitro* effects**									
Anabasine	Alkaloid	*Nicotiana glauca*	——	−[y], =[z]					
Nicotine	Alkaloid	*Nicotiana* spp.	——	=[k], =[y]	=[i]				
Gelsemine	Alkaloid	*Gelsemium sempervirens*	——	=[h]					
Eugenol	Allylbenzene	Multiple plant families	——	−[y], −[aa]					
Amygdalin	Cyanogenic glycoside	*Prunus* spp.	——	=[y]					
Caffeic acid	Hydroxy-cinnamic acid	Multiple plant families	——	=[y]					
Gallic acid	Hydroxy-cinnamic acid	Multiple plant families	——	=[y]					
Aucubin	Iridoid glycoside	Multiple Asterids	–	−[z]					
Catalpol	Iridoid glycoside	Multiple Lamiales families	——	=[z]					
Beta-caryophyllene	Sesquiterpene	Multiple plant families	——	=[y]					
Carvacrol	Terpenoid	Lamiaceae	——						−[ab]
Geraniol	Terpenoid	Lamiaceae	——						=/−[ab]
Linalool	Terpenoid	Lamiaceae	——						=/−[ab]
Thymol	Terpenoid	Lamiaceae	——	−[y], =[z], −[aa], =[ac]					−[ab]
α-Terpineol	Terpenoid	Lamiaceae	——						=/−[ab]
trans-Sabinene hydrate	Terpenoid	Lamiaceae	——	−[y], −[aa], =[ac]					=/−[ab]

(*continued on next page*)

Table 1 (*continued*)

Floral product or metabolite	Metabolite type	Source plant(s)	Host species	Parasite					
				Crithidia bombi	*Nosema* sp.	*Lotmaria passim*	Deformed wing virus	Other viruses	Pathogenic bacteria
Geranyl acetate	Terpene acetate	Lamiaceae	—						= [ab]
Linolyl acetate	Terpene acetate	Lamiaceae	—						= [ab]
Terpenyl acetate	Terpene acetate	Lamiaceae	—						= [ab]

+ indicates positive effect of floral product on parasite load; = indicates no effect; – indicates negative effect. Commas separate studies; a slash indicates that effect of floral product varied across treatments within a study (e.g., with variation in environmental conditions, across sexes or life stages of host, or among genotypes of either host or parasite). Superscripts indicate references.

[a] Anthony et al. (2015).
[b] Richardson et al. (2015).
[c] Thorburn et al. (2015).
[d] Bernklau et al. (2019).
[e] Lu et al. (2020).
[f] Hsieh et al. (2020).
[g] Folly et al. (2021).
[h] Manson et al. (2010).
[i] Hendriksma et al. (2020).
[j] Biller et al. (2015).
[k] Baracchi et al. (2015).
[l] Tauber et al. (2020).
[m] Adler et al., 2020.
[n] Folly et al. (2020).
[o] Costa et al. (2010).
[p] Szawarski et al. (2019).
[q] Maistrello et al. (2008).
[r] Koch et al. (2019).
[s] Gherman et al. (2014).
[t] Giacomini et al. (2018).
[u] LoCascio et al. (2019a).
[v] LoCascio et al. (2019b).
[w] Fowler et al. (2020).
[x] Giacomini et al., 2021.
[y] Palmer-Young et al. (2016).
[z] Michaud et al. (2019).
[aa] Palmer-Young et al., 2017.
[ab] Wiese et al. (2018).
[ac] Rothchild et al. (2018).

microbial infection (Jeandet et al., 2010). Ten structurally related stilbenes that varied in their hydroxylation and methoxylation were tested for bioactivity against three species of the genus *Leishmaniasis*, which are trypanosomes like *C. bombi*, but infect mammals. These species showed highly variable sensitivity to the different stilbenes, with LD_{50} activity ranging from 2 μg/ml to 300 μg/ml, despite the compounds' structural similarity (Getti et al., 2006). Thus, while some compounds have highly potent antimicrobial activity, others, even those with similar structures, do not. At this point, we can make few generalizations about the role different classes of metabolites play in the antiparasitic activity of floral products – other than that any attempt at generalization is unlikely to be accurate.

Even within a single metabolite type, minor structural modifications can have profound effects on bioactivity. For example, only aglycones of the antimicrobial isoflavenes in wild chickpea (*Cicer bijugum*) are active against the fungal pathogen *Fusarium oxysporum* f. sp. *ciceri.* In response to fungal attack, therefore, the plant cleaves the sugar residue. Yet while the aglycones have strong antifungal effects, different substitutions on the ring of isoflavenes and aryl benzofurans lead to dramatic differences in activity against *Fusarium* (Stevenson and Veitch, 1998). Similarly, the inhibitory effects of plant compounds on bee parasites can be highly influenced by glycosylation and deglycosylation in the gut (Koch et al., 2022; see Section 3.3).

Inhibitory effects of the same or related compounds also differ between target microorganisms. While caffeine is not biologically active against *C. bombi* (Richardson et al., 2015), it inhibits a microsporidian parasite of bumble bees, *Nosema bombi* (Folly et al., 2021), and the closely related *N. ceranae,* which infects honey bees (Bernklau et al., 2019). Furthermore, variation in response to a compound across genotypes within a species provides an additional nuance to understanding bioactivity. For example, while the monoterpene thymol is biologically active against *C. bombi*, different strains of this parasite differ in their response to the compound (Palmer-Young et al., 2016). This may be due in part to evolved resistance to thymol in parasite lineages with a previous history of exposure: in another study, *C. bombi* lineages chronically exposed over 6 weeks to thymol and eugenol, either alone or in combination, developed resistance to the compound(s) to which they were exposed (Palmer-Young et al., 2017a). However, the ability of parasites to evolve resistance is likely to vary across floral products; for example, in contrast to Palmer-Young et al. (2017a), Giacomini et al. (2021b) found no evidence for evolved resistance to sunflower pollen in *C. bombi* after 10 weeks of exposure *in vivo*. This variation is likely due to differences in the mechanism underlying the antiparasitic effect, reiterating the importance of improving mechanistic understanding for our ability to predict the dynamic relationships among host, parasite, and antiparasitic food plants.

In light of the specificity of activities of plant metabolites against parasites, we advocate for research that describes the specific chemical components of floral products and their individual biological activities, rather than investigating associations between broader classes of metabolites and bioactivity against parasites.

3.2. Nonadditive effects of multiple phytochemicals on bee parasites

A common approach in floral product–bee disease research has been to assess the influence of a single phytochemical, either on cultures *in vitro* or within the host. Yet nectar and pollen from a single species of plant generally contain a diversity of phytochemicals (Palmer-Young et al., 2019). Moreover, it is common for pollinators to consume, and provision larvae with, nectar and/or pollen from multiple species within a short timeframe. This means that pollinator parasites may be exposed to a complex concoction of different phytochemicals, and raises the question of whether findings derived from studies of single phytochemicals in isolation can be extrapolated to natural conditions. Nonadditive effects of multiple phytochemicals on bee parasites have rarely been investigated; where they have been looked for, they have generally been found, including both synergistic (Biller et al., 2015; Palmer-Young et al., 2017b) and antagonistic (Thorburn et al., 2015) effects. Looking beyond bee parasites, a review of the effects of combinations of essential oils or their constituent volatiles on bacteria and fungi found roughly equal numbers of additive and synergistic effects, with markedly fewer antagonistic effects reported (Bassolé and Juliani, 2012).

The prevalence of nonadditive effects suggests that the common approach of testing single phytochemicals risks missing substantial effects of floral products on bee parasites, and potentially underestimating the importance of these effects on patterns of pollinator disease in natural conditions. More accurate assessments will require consideration of nonadditive effects. At the same time, a key area for growth in the field of pollinator disease is improving our understanding of the mechanisms underlying floral product effects on parasites. At first glance, these two goals appear likely to conflict, since the controlled experimentation required to uncover physiological and biochemical mechanisms is often only possible using simplified phytochemical profiles. But an improved understanding of the mechanistic basis for the antiparasitic effect of one metabolite may help us predict how it will interact with other compounds. Clearly, there is a need for both studies that explicitly consider nonadditive effects of complex mixtures of phytochemicals, and those that explore the mechanistic basis of effects of specific floral products or their constituent phytochemicals. A particularly fruitful approach may be to integrate both approaches, assessing the effects of complete floral products or combinations of floral products, and then taking a more reductionist approach to identify the specific compound(s) responsible for observed effects, and their mechanistic basis (e.g., Koch et al., 2019).

We advocate for studies of nonadditive effects to be founded, where possible, in knowledge of biochemical mechanism and/or patterns of phytochemical co-occurrence in the field. For example, the antimicrobial effects of some terpenoids stem from their role in membrane disruption (Bassolé and Juliani, 2012; Chavan and Tupe, 2014; Xu et al., 2008). Given their similar effects, combinations of these compounds might be expected to have additive or sub-additive effects. But combining a membrane disruptor with a compound that, for example, interacts with proteins within the cytoplasm [e.g., eugenol (Pei et al., 2009)] would be more likely to yield synergistic effects. Experiments guided by an understanding of the biochemical effects of compounds are particularly likely to yield generalizable insight into nonadditive effects. At the same time, from an ecological perspective, strong nonadditive effects from combinations of phytochemicals are no more than curiosities if those combinations are unlikely to be encountered by foraging bees or provisioned to developing larvae. Understanding the foraging ecology of bees and the composition of nectar and pollen metabolites can help guide us to phytochemical combinations that are most likely to occur, and therefore are of greatest interest to understanding the effect of floral products on parasite dynamics. One rather surprising pattern uncovered by Bassolé and Juliani (2012) in their review of nonadditive effects of essential oils on foodborne pathogens was that synergistic effects were more common when testing combinations of volatile compounds, while additive effects preponderated in combinations of complete essential oil profiles from multiple plant species. Determining whether this pattern holds across floral products containing other classes of phytochemicals beyond essential oils would be instructive.

3.3. Phytochemical transformation through host digestion and absorption

Knowing the chemical composition of pollen and nectar, and the direct effects of phytochemicals on parasites of bees (e.g., through *in vitro* tests), does not necessarily allow conclusions about their effects on parasites in the bee itself. Secondary metabolites of nectar and pollen can undergo chemical transformations after ingestion by bees, or can vary in their absorption from the gut (Vidkjær et al., 2021). This can lead to internal parasites being exposed to metabolites that differ substantially from those found in the uningested floral product. Furthermore, in bee species that collect and store nectar and pollen, phytochemicals may also change pre-ingestion – for example in stored pollen (Loper et al., 1980) and nectar/honey (Liu et al., 2005; Naef et al., 2004) of social corbiculate bees, and potentially in pollen provisions for larvae of solitary bees (Steffan et al., 2019). While recognizing this potential, for the rest of this section we focus on post-ingestion processes. Although post-ingestion transformation of phytochemicals is host-mediated, we include this topic within direct effects, since it is still the compounds themselves that affect the parasite. That said, phytochemicals can also influence host digestion and metabolism in ways that inhibit parasite infection; we discuss these effects in sections 4.1 and 4.3.

Transformation of secondary metabolites in the bee gut can occur via the activity of endogenous host enzymes secreted into the gut. For example, honey bees produce cytochrome P450 (CYP) enzymes that can detoxify a range of dietary secondary metabolites (Berenbaum and Johnson, 2015), including nectar nicotine (du Rand et al., 2017, 2015). Catabolism of secondary metabolites by enzymes in the gut is likely to reduce their toxicity to both the host and the infecting parasites.

Alternatively, enzymes produced by resident microbial associates in the insect gut (the gut microbiome) can transform dietary metabolites. The microbiome appears to play important roles in modifying phytochemicals, especially where hosts lack the enzymes for catalyzing relevant reactions (Ceja-Navarro et al., 2015; van den Bosch and Welte, 2017; Zheng et al., 2016). Honey bees and bumble bees harbor a specific resident microbiome (Kwong et al., 2017), the composition of which is known to affect outcomes of parasite infections (Koch and Schmid-Hempel, 2011; Rubanov et al., 2019). Kešnerová et al. (2017) demonstrated that some members of this gut microbiome, including lactic acid bacteria and bifidobacteria, play a key role in catabolizing pollen flavonoid glycosides, including initial deglycosylation. Similarly, recent research has shown that the deglycosylation of unedone-glucoside from strawberry tree (*Arbutus unedo*) nectar in the bumble bee hindgut (see additional detail below) is the result of gut microbial activity (Koch et al., 2022). This suggests that the gut microbiome has the potential to both increase and decrease the activity of pollen and/or nectar secondary metabolites against parasites, depending on the form of the relevant metabolites in the floral product.

The degree to which these transformations matter in determining the antiparasitic effects of floral products will depend on the site of infection of the relevant parasite within the host body, and the type and location of the transformation. The site of infection varies across parasite species, and includes the gut lumen [e.g., the trypanosomatids *C. bombi* in the hindgut of bumble bees (Koch et al., 2019) and *Lotmaria passim* in the pylorus of honey bees (Schwarz et al., 2015)]; intracellularly in one or more tissues [e.g., the microsporidian *Nosema ceranae* in the midgut tissue of honey bees (Huang and Solter, 2013)]; the haemocoel [e.g., the nematode *Sphaerularia bombi* in bumble bees (Madel, 1973)]; or throughout the body [e.g. viruses including DWV (de Miranda and Genersch, 2010)]. For parasites located in the gut, transformation or absorption of anti-parasitic metabolites anterior to their infection site will reduce or prevent parasite exposure to the metabolite. For parasites in the haemocoel, absorption of metabolites through the gut wall into

the body cavity will define their exposure. Direct exposure of intracellular parasites, in turn, requires uptake of the relevant metabolite(s) by host cells in the infected tissues. Chemical transformation of phytochemicals may increase or decrease their anti-parasitic activity and ability to be absorbed through the gut wall or cell membranes.

So far, explicit studies of the fate of secondary metabolites in bees in combination with their effect on parasites are rare. Some recent studies, however, suggest that investigating these processes in the host can provide valuable insights into how and why pollen and nectar metabolites have anti-parasitic activity. In one example, Koch et al. (2019) showed that callunene, a secondary nectar metabolite of heather, inhibits *C. bombi in vitro* at concentrations found naturally in nectar. Tracking callunene concentrations through the different gut compartments, they showed that concentrations in the crop were similar to nectar concentrations, but callunene concentrations rapidly fell from the midgut to the hindgut. Consequently, callunene did not reach the site of infection of *C. bombi* in the hindgut, and feeding on callunene had no effect on the infection status of already-infected bees. However, brief exposure to callunene *in vitro*, at the concentration likely experienced by newly ingested parasites in the crop of bumble bees foraging on heather nectar, induced a loss of the parasite flagellum, and subsequently reduced infection probability (Koch et al., 2019). Studying the fate of callunene provided insight into why callunene can act prophylactically against *C. bombi* infections, but fails to cure existing infections.

In another study of the interaction between secondary metabolite conversion and infections with *C. bombi* in bumble bees, Koch et al. (2022) showed that the glycosylation status of two nectar metabolites changed during gut passage, and that glyocosylation status in turn determined the anti-*Crithidia* activity of both metabolites. Unedone in strawberry tree nectar and 1-[4-(1-hydroxy-1-methylethyl)-1,3-cyclohexadiene-1-carboxylate]-6-*O*-*β*-D-glucopyranosyl-*β*-D-glucopyranose (tiliaside) in linden (*Tilia*) nectar both had low activity against *C. bombi* as glycosides, but high activity as aglycones. While unedone was glycosylated to unedone-8-*O*-*β*-D-glucoside in the midgut, thus reducing its effect on hindgut-infecting *C. bombi*, tiliaside was deglycosylated during gut passage, resulting in higher activity once it reached *C. bombi* in the hindgut. However, the unedone-8-*O*-*β*-D-glucoside produced in the midgut was again deglycosylated in the bumblebee hindgut in the presence of the resident microbiome, thereby restoring its antiparasitic activity.

Despite the evident value of these approaches, multiple factors complicate our efforts to understand how the transformation and absorption of phytochemicals post-ingestion may influence their antiparasitic activity. First, the nature of phytochemical transformation and absorption likely varies across pollinator species, genotypes, life stages, sexes, or individuals colonized with different microbial communities. This may result in different effects of dietary phytochemicals on individual pollinators belonging to different categories, and could explain differences in experimental results. For example, the isoflavonoid biochanin A in clover (*Trifolium*) pollen reduced *Nosema* infections when fed to adult *B. terrestris* workers, but not larvae (Folly et al., 2020). Folly et al. (2020) did not demonstrate differences in metabolite transformation and/or absorption across life stages, but suggest it as a potential explanatory mechanism.

Second, changes to the bee gut microbiome through anthropogenic effects may influence the conversion and activity of nectar and pollen secondary metabolites. Both the herbicide glyphosate (Motta et al., 2018) and the heavy metals and industrial pollutants cadmium and selenate (Rothman et al., 2019) affected the composition of the honey bee microbiome [and, in the case of glyphosate at least, increased susceptibility to pathogens (Motta et al., 2018)]. Antibiotic treatment of honey bee colonies reduces the resident core microbiome (Raymann et al., 2018), and affects protein digestion (du Rand et al., 2020). It is certainly likely, though not yet demonstrated, that such anthropogenic alteration to the microbiome would affect the fate of ingested phytochemicals and their impact on parasites. Further research on how phytochemicals are transformed and absorbed post-ingestion, with a focus on following the fate of the same phytochemical across multiple pollinator categories and across gradients of exposure to anthropogenic chemicals, is needed before we can understand the magnitude and prevalence of such differential effects. In the meantime, caution is warranted in any attempt to extrapolate findings beyond the specific system under study.

4. Host-mediated effects

Thus far, we have discussed antiparasitic effects of floral products that stem directly from the impact of phytochemicals on parasites. We turn next to considering host-mediated effects. Host-mediated effects occur when a floral product consumed by an infected host influences one or more component of the host's biology, in a way that then leads to parasite inhibition, independent of the effect of the floral product directly on the parasite. Such host-mediated effects include those where the floral product influences host digestion and excretion, host immune system, and host microbiome. Below, we present the evidence for the operation of each type of host-mediated effect, and discuss approaches to distinguishing among them.

Distinguishing between direct and host-mediated effects is not necessarily easy. In cases where a floral product reduces infection in the host but does not affect parasite growth *in vitro* (e.g., Manson et al., 2010), the effect is clearly host-mediated. But in cases where effects are observed both *in vitro* and *in vivo*, ascribing the effect to a particular mechanism is less straightforward for several reasons. First, it may not be appropriate to compare the effects of the relevant product between *in vitro* and *in vivo* treatments, since the host may metabolize or otherwise transform compounds in the raw floral product before the parasite is exposed within the host (see Section 3.3), and how this occurs is likely to be idiosyncratic across floral products and host species. Second, reduced direct effects may be masked by host-mediated effects, such that even if the same degree of parasite inhibition is observed in both culture and host, the underlying mechanism may be different. Thus, in cases where effects are observed both *in vitro* and *in vivo*, further experimentation is required to unequivocally determine whether effects are direct or host-mediated, or a combination of the two. Moreover, multiple aspects of host biology may mediate the diet-disease connection. Recent advances in transcriptomics and bioinformatics present tremendous opportunities, when paired with creative experimental design, to tease apart the contributions of direct and host-mediated effects. This understanding may, in turn, shed light on fundamental questions about the role of the immune system and microbiota in determining bee health.

4.1. Host digestion and excretion-mediated effects

Floral products could influence host digestion and excretion in ways that reduce parasite infection intensity or duration, especially with parasites that have fecal-oral transmission and infect the bee gut. This could occur via at least two non-exclusive mechanisms. First, floral products may affect gut passage time or excretion rate (Giacomini et al., 2022; Tadmor-Melamed et al., 2004). Floral products that act as laxatives may reduce the ability of ingested parasites to infect the host, given that time is needed for the parasite to infect the appropriate tissue. While such an effect has not been demonstrated unequivocally, suggestive evidence exists. Sunflower (*Helianthus annuus*) pollen dramatically reduces *C. bombi* infection levels in *B. impatiens* (Fowler et al., 2020; Giacomini et al., 2018; LoCascio et al., 2019a), and also reduces gut passage time (Giacomini et al., 2022). We note in passing, however, that laxative diets have the potential to increase parasite shedding in infected hosts, a complication that highlights the need to consider both within-host and between-host parasite dynamics to fully understand the net effect of a floral product on pollinator parasites and pollinator health.

Floral products, particularly pollen, may also interact with digestion

processes to mechanically disrupt gut parasites. The outer shell, or exine, of pollen is not digested, and generally passes through the gut intact or as crushed fragments (Dobson and Peng, 1997; Peng et al., 1985; Suárez-Cervera et al., 1994). In some species (e.g., many Asteraceae), the exine includes spines or other protruding structures (Blackmore et al., 2007) which, on passage through the gut, might scour parasites that are lodged in the gut lining (e.g., trypanosomatids like *Crithidia* and *Lotmaria*). While the effectiveness of sunflower and some other Asteraceae at reducing *Crithidia* infection in bumble bees (Giacomini et al., 2018, 2021b; LoCascio et al., 2019a) is consistent with this hypothesis, other explanations for the inhibitory effect of sunflower pollen exist, and mechanical effects have not been unequivocally demonstrated. There are several potential approaches to isolating mechanical from chemical effects of pollen. One possibility is to compare the effect of crushed and intact pollen grains, with the idea that crushing pollen grains may eliminate mechanical defenses (Brochu et al., 2020; Vanderplanck et al., 2020). However, Vanderplanck et al. (2020) found enhanced damage to the gut lining in bumble bees fed crushed compared to intact dandelion (*Taraxacum officinale*) pollen, suggesting that crushing may not eliminate or even reduce mechanical defenses. As an alternative, intact exines could be extracted from whole pollen grains using acidolysis (Domínguez et al., 1998; Fan et al., 2018) to remove the potential effect of chemical components, and these exines could then be added to a control pollen diet. If future work with sunflower and other Asteraceae confirms the importance of mechanical effects in parasite inhibition, it would be interesting to look for such effects in other mechanically-defended pollen, such as from flowers in the Malvaceae (Lunau et al., 2015).

4.2. Host immune-mediated effects

In addition to altering digestion and excretion, floral products can affect host immune response, for example by influencing immune gene expression. To date, only a few studies have investigated links between diet, immune response, and disease in pollinators. While the insect immune system includes multiple components (reviewed in Gillespie and et al., 1997; Rolff and Reynolds, 2009), most of the existing studies on diet effects have focused on antimicrobial peptides (AMPs) and signaling genes in the Toll and Imd pathways, which regulate AMP production. AMPs are ubiquitous in arthropods, including bees (Bulet et al., 1999), and play an important role in immune response. For example, AMPs reduce trypanosome infection in multiple insect species (Boulanger et al., 2006), including bumble bees (Marxer et al., 2016), and trypanosome infection can lead to upregulation of AMPs (Boulanger et al., 2006).

Studies that have looked for effects of phytochemicals on immune gene expression have generally found them, though nearly all such studies have used the western honey bee (Boncristiani et al., 2012; Lu et al., 2020; Mao et al., 2013; Palmer-Young et al., 2017c). Compound classes that influence immune gene regulation include alkaloids (Lu et al., 2020; Palmer-Young et al., 2017c), terpenoids (Boncristiani et al., 2012; Palmer-Young et al., 2017c), phenolic acids (Mao et al., 2013; Palmer-Young et al., 2017c), and iridoid glycosides (Palmer-Young et al., 2017c), with two studies finding no effect of the cyanogenic glycoside amygdalin on AMP expression (Palmer-Young et al., 2017c; Tauber et al., 2020). Most studies document a positive relationship between phytochemical consumption and immune gene expression (Lu et al., 2020; Mao et al., 2013; Palmer-Young et al., 2017c), suggesting an immune-boosting effect of phytochemical consumption, but Boncristiani et al. (2012) found that thymol exposure downregulated immune recognition and signaling, although AMP production was unaffected. Recent work focusing on whole sunflower pollen, rather than constituent metabolites, found that *B. impatiens* individuals infected with *C. bombi* and fed sunflower pollen exhibited enhanced expression of AMP *hymenoptaecin* and Toll receptors in gut tissue, compared to infected bees fed wildflower pollen (Giacomini et al., 2021a). Interestingly, however, sunflower pollen consumption did not affect antibacterial activity in *B. impatiens* hemolymph (Fowler et al., in press), suggesting tissue-specific effects of floral products on immune response. These studies strongly indicate that consumption of a diversity of phytochemicals found in nectar and pollen can influence immune response.

Evidence that effects on immune response translate into disease reduction is more limited. Only two studies have simultaneously evaluated effects of diet on immune gene expression and parasite infection in bees; in both studies, the addition of phytochemicals to the diet increased immune activity and reduced deformed wing virus (DWV) infection (Lu et al., 2020; Palmer-Young et al., 2017c). However, Palmer-Young et al. (2017b) additionally assessed *Nosema* and *Lotmaria* infection, and found no effect of any of the tested phytochemicals on infection intensity of those parasites, suggesting that immune system-mediated effects of phytochemicals may not be generalizable to multiple bee pathogens. Alternatively, the link between phytochemical consumption and virus inhibition may not be mediated by immune response, but rather by another mechanism (e.g., direct chemical effects); these studies do not allow us to conclusively identify the underlying mechanism.

Isolating immune system-mediated effects of diet is challenging. One approach, analogous to that used by Marxer et al. (2016), is to measure the production of select peptides of interest under different diet treatments, and then use synthesized peptides to evaluate the effects of peptide concentrations recovered from diet treatments on parasite cultures *in vitro*. While promising, this approach is limited by the availability of sequence data [although AMP sequences appear to be highly conserved across species, easing this limitation (Barribeau et al., 2015)]. More importantly, such a reductionist approach assesses the effects of isolated components of the immune system, and disregards the potential for interactions among immune system components or between immune response and other aspects of host physiology (Little et al., 2005). Thus, while this approach holds promise for elucidating the effect of diet on specific peptides of interest, other approaches will be needed to understand the full scope of the diet-immune function-disease relationship in bees. Moreover, research on species other than *A. mellifera* is sorely needed, but hampered by our relatively rudimentary understanding of non-honey bee immune systems.

4.3. Host microbiome-mediated effects

Host microbiome-mediated effects occur when the floral product influences the composition or activity of the host's non-pathogenic microbiome in a way that reduces parasite infection. To our knowledge, a causal link between host diet and disease resistance mediated by host microbiome has yet to be unequivocally demonstrated in any system, but there is suggestive evidence. Multiple studies have demonstrated that diet, including plant metabolites, influences microbiome composition in both solitary and social bees (Billiet et al., 2016; Geldert et al., 2021; Maes et al., 2016; Voulgari-Kokota et al., 2020), and microbiome composition can influence disease resistance (Koch and Schmid-Hempel, 2011, 2012; Mockler et al., 2018; Rubanov et al., 2019; Wu et al., 2020). Maes et al. (2016) demonstrated diet-related shifts in the honey bee microbiome, and further found an association between microbiome composition and *Nosema* infection, but the relationship between diet and parasite infection could also arise from direct chemical effects or immune system-mediated effects. Unequivocal confirmation of microbiome-mediated effects of floral products on disease will require microbiota transplant experiments (from individuals feeding on the floral product of interest to parasite-exposed individuals fed a control diet), to isolate the effect of diet on the microbiome from its other potential effects (Harris et al., 2019). To our knowledge, no such study has been published. Moreover, a recent study comparing immune gene expression and *Nosema* infection between gut microbiota-deficient and control *A. cerana* showed elevated expression of multiple immune genes in bees with control microbiota (Wu et al., 2020). These bees also had

reduced *Nosema* spore loads, suggesting that the association between microbiome and disease may be mediated by the effects of the gut microbiota on immune response (Wu et al., 2020). This study highlights the importance of considering how floral products may simultaneously influence multiple aspects of host biology; we are excited for future research that deepens our understanding of the relationship between the immune system and the microbiome in bees, and how this relationship is shaped by floral products.

5. The influence of antiparasitic effects of floral products on bee-parasite dynamics in natural conditions

Our ability to understand the magnitude of antiparasitic effects of floral products in natural conditions is vital to a complete understanding of bee-parasite dynamics, especially in the context of pollinator management and bee conservation efforts. To date, the majority of work evaluating the effects of floral products on bee disease dynamics has been conducted in the laboratory. There are far fewer studies that have demonstrated effects under field conditions. In one example from Belgium, the occurrence of the non-native plant *Impatiens glandulifera* was associated with lower prevalence of the Neogregarine pathogen *Apicystis bombi* (though not of *C. bombi* or *Nosema* spp.) in wild *B. pascuorum*. The authors propose that this correlation may be due to the richness of polyphenols found in the pollen of *I. glandulifera*, which could have inhibited *A. bombi*, though this hypothesis was not explicitly tested (Vanderplanck et al., 2019). In another, Giacomini et al. (2018) found, in addition to striking inhibitory effects of sunflower pollen on *C. bombi* in laboratory assays, a negative correlation between the total area of cultivated sunflower and *C. bombi* infection intensity of wild-caught *B. impatiens* workers across 22 farms. Similar patterns were found for initially pathogen-free commercial *B. impatiens* colonies deployed in farms that varied in the number of sunflower flower heads present (Malfi et al., unpublished data). However, in another recent study in commercial sunflower farms, *C. bombi* prevalence in wild caught bees (of multiple genera) trended higher in plots that were adjacent to sunflower fields compared to plots with no sunflower adjacent (Cohen et al., 2021). This mixed evidence highlights the complexity of evaluating the effect of antiparasitic floral products in field conditions, where a multitude of other factors are operating to shape patterns of bee parasite prevalence and disease.

One such factor is the availability and spatial configuration of floral resources at both local and landscape scales. This can shape bee parasite dynamics in multiple ways, including by influencing bee abundance and density (and therefore parasite transmission) and bee nutritional status (and therefore ability to tolerate and/or defend against parasites). Several studies have documented correlations between pathogen prevalence in bees and total floral resource availability. Piot et al. (2019) found that in landscapes with little semi-natural habitat (i.e., resource-poor landscapes), adding a wildflower planting increased the prevalence of multiple parasites of *B. pascuorum* (*A. bombi*, *C. bombi*, and *N. bombi*, but not viruses), and the size of the planting was also positively correlated with parasite prevalence. In high-resource landscapes, on the other hand, the presence and size of wildflower plantings did not influence pathogen prevalence. The authors suggest this pattern could result either from the improved nutritional status of bees in flower-added landscapes leading to better tolerance of parasites, or from the concentration of bees at small, resource-rich sites leading to high parasite transmission (Piot et al., 2019). Similarly, in commercial sunflower plantings in California, USA, high bee abundance was linked to greater parasite prevalence at sites with low-to-average floral abundance, but to reduced parasite prevalence at sites with high floral abundance (Cohen et al., 2021). And in another study across multiple habitats and two years in Pennsylvania, USA, the prevalence of *N. bombi* and several pathogenic viruses in *B. impatiens* was negatively correlated with the availability of early-season floral resources (McNeil et al., 2020). In contrast, Graystock et al. (2020), surveying multiple parasites across the entire bee community in three meadows in New York, USA, found that parasite prevalence in bees was more strongly influenced by bee community composition than it was by floral resource availability *per se* (though the bee community was likely influenced by floral resources).

The timing and duration of exposure to antiparasitic floral products can strongly influence the strength of their inhibitory effects, as we have already seen with the example of callunene in heather nectar (Koch et al., 2019). In another example, while the consumption of sunflower pollen over the span of one week dramatically reduced *C. bombi* infection in *B. impatiens* workers, sunflower pollen consumption limited to a 3.5 day period had less inhibitory effect, particularly if consumption was delayed for several days after initial infection (LoCascio et al., 2019b). Moreover, one-time consumption of sunflower pollen at the time of infection had no effect on ultimate infection intensity (LoCascio et al., 2019b). Thus, the presence of antiparasitic floral products in the environment – and even the consumption of those products by a bee – does not necessarily mean that antiparasitic effects will manifest in the bee. This will depend on the foraging behavior of the bee, which determines the amount and timing of exposure to the relevant floral products. Foraging behavior is, in turn, influenced by the composition and density of both pollinator and flowering plant communities, suggesting that we should not expect equivalent effects of the same antiparasitic plant species across environmental contexts.

Parasites under chronic exposure to antiparasitic compounds can rapidly evolve resistance to these compounds, as has been shown in lab experiments with *C. bombi* (Palmer-Young et al., 2018, 2017a; but see Giacomini et al., 2021b). While the levels of sustained exposure necessary to drive the evolution of resistance are less likely to occur in the field, this will depend on the composition of floral resources and bee foraging behavior. It is therefore worth investigating whether the effects of particular antiparasitic plant species attenuate over time, especially in environments where they occur at high abundances and are heavily foraged by bees.

Infection status could alter bee foraging behavior to favor species with antiparasitic effects. Such 'self-medicating' behavior has been documented in other insects, most notably the Lepidopteran woolly bear caterpillar (*Grammia incorrupta*) (Bernays and Singer, 2005; Singer et al., 2009); there is suggestive evidence for similar behavior in bees (Gherman et al., 2014; Richardson et al., 2016), but this has yet to be conclusively demonstrated. If infected bees preferentially feed on flowers that reduce parasite infection, we might expect that this would enhance the population-level signal strength of antiparasitic floral products on parasite prevalence. Moreover, the question of whether bees self-medicate has important implications for pollinator conservation efforts. Several recent studies documenting antiparasitic effects of pollen or nectar of specific plant species advocate for increased planting of these species as a strategy for managing disease and promoting bee populations (Folly et al., 2021; Giacomini et al., 2018). Setting aside broader questions regarding the utility of this approach (Fowler et al., 2022; Palmer-Young et al., 2017a), its impact will depend heavily on whether bees self-medicate. That is, a given increase in the availability of 'medicinal' plant species will have a much larger effect on parasite dynamics if infected bees preferentially forage on plants that reduce infection. While data are lacking, the degree to which bees self-medicate may make the difference between a feasible and effective management intervention and an impractical one. Therefore, rigorous evaluation of the extent to which bees self-medicate is an essential research need. This will require investigating the effect of infection on bee foraging preferences in both lab and field settings.

Finally, it is important to consider how other aspects of floral biology, beyond the antiparasitic effects of floral products, may influence patterns of bee disease. In particular, flowers of different species differ in their competence as sites of parasite transmission (Figueroa et al., 2019). For example, while pollen from two species of goldenrod (*Solidago rugosa* and *S. canadensis*, in the same family as sunflower) had

C. bombi-inhibitory properties in laboratory assays performed with *B. impatiens* (LoCascio et al., 2019a), *S. canadensis* was also found to be a "high infection" plant when bees were allowed to forage freely and encounter experimentally placed droplets of *C. bombi* inoculum on inflorescences (Adler et al., 2018). In a subsequent study, which varied the proportion of "low infection" and "high infection" flowers (including the goldenrod *S. altissima altissima*) in replicated tents, *C. bombi* infection intensity in *B. impatiens* microcolonies in "high infection" tents was nearly double that seen in "low infection" tents (Adler et al., 2020a). This is a clear example of how the signal of antiparasitic effects of floral products may be obscured in natural systems by countervailing effects of the relevant plant species on other determinants of disease, including bee nutritional state and parasite transmission dynamics. Few studies have evaluated the relationship between bee disease dynamics and floral resources in the field, limiting our ability to make predictions about how the presence of particular floral resources influences parasite prevalence across the bee community and through time. An important future direction is to evaluate the intersection of the pathogen-inhibitory properties of nectar and pollen with the differential transmission potential of their source flowers, within realistic nutritional contexts.

Given our currently limited mechanistic understanding of the ways many floral products influence bee disease dynamics, researchers can benefit from the structure employed by the medical research community, where the antiparasitic effect of specific chemicals are first tested *in vitro*, then *in vivo* (on model organisms), and finally in clinical studies. This structure is helpful since *in vitro* experimentation represents an efficient way to screen a wide range of floral products for antiparasitic effects, with the understanding that antiparasitic effects *in vitro* do not always translate to effects in the host. Therefore, promising candidates from *in vitro* experiments can then be evaluated *in vivo* in multiple host species, and lastly in field-realistic settings.

6. Conclusion

There is evidence that floral products can have both prophylactic and therapeutic effects on bee disease. But much remains to be learned about the mechanisms underlying antiparasitic effects, the causal factors leading to specificity in effects across both host and parasite species and genotypes, and the eco-evolutionary significance of these antiparasitic effects in natural communities. Particularly useful avenues for future research include:

- Understanding the mechanistic basis of antiparasitic effects, through experiments that distinguish among potential mechanisms and seek to understand the biochemical and/or physiological effects of floral products and their constituent metabolites on both host and parasite.
- Expanding the scope of study to consider more host and parasite species. In particular, research is needed on non-corbiculate bees and non-trypanosomatid parasites.
- Evaluating the effects of parasite infection on bee foraging behavior, and in particular the potential for bees to 'self-medicate' by preferentially feeding on antiparasitic floral products when faced with infection.
- Using 'natural experiments' or manipulations of conditions in the field to evaluate the magnitude of antiparasitic effects of floral products on bee-parasite dynamics in populations and communities while also considering the role of flowers in transmission. Particular attention will need to be paid to methods that allow us to distinguish among the multiple ways in which floral resource availability, morphology and composition influence patterns of parasite prevalence and transmission.

We anticipate that such research – as well as research directions that move beyond what we outline here – will dramatically improve our understanding of the significance of antiparasitic floral products for plant-pollinator-parasite dynamics, and highlight new avenues to further pollinator conservation.

Declaration of competing interest

None.

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References

Adler, L.S., 2000. The ecological significance of toxic nectar. Oikos 91, 409–420. https://doi.org/10.1034/j.1600-0706.2000.910301.x.

Adler, L.S., Barber, N.A., Biller, O.M., Irwin, R.E., 2020a. Flowering plant composition shapes pathogen infection intensity and reproduction in bumble bee colonies. Proc. Natl. Acad. Sci. Unit. States Am. https://doi.org/10.1073/pnas.2000074117.

Adler, L.S., Fowler, A.E., Malfi, R.L., Anderson, P.R., Coppinger, L.M., Deneen, P.M., Lopez, S., Irwin, R.E., Farrell, I.W., Stevenson, P.C., 2020b. Assessing chemical mechanisms underlying the effects of sunflower pollen on a gut pathogen in bumble bees. J. Chem. Ecol. 46, 649–658. https://doi.org/10.1007/s10886-020-01168-4.

Adler, L.S., Michaud, K.M., Ellner, S.P., McArt, S.H., Stevenson, P.C., Irwin, R.E., 2018. Disease where you dine: plant species and floral traits associated with pathogen transmission in bumble bees. Ecology 99, 2535–2545. https://doi.org/10.1002/ecy.2503.

Anthony, W.E., Palmer-Young, E.C., Leonard, A.S., Irwin, R.E., Adler, L.S., 2015. Testing dose-dependent effects of the nectar alkaloid anabasine on trypanosome parasite loads in adult bumble bees. PLoS One 10, 1–13. https://doi.org/10.1371/journal.pone.0142496.

Arnold, S.E.J., Dudenhöffer, J.-H., Fountain, M.T., James, K.L., Hall, D.R., Farman, D.I., Wäckers, F.L., Stevenson, P.C., 2021. Bumble bees show an induced preference for flowers when primed with caffeinated nectar and a target floral odor. Curr. Biol. 31, 4127–4131. https://doi.org/10.1016/j.cub.2021.06.068 e4.

Arnold, S.E.J., Idrovo, M.E.P., Arias, L.J.L., Belmain, S.R., Stevenson, P.C., 2014. Herbivore defence compounds occur in pollen and reduce bumblebee colony fitness. J. Chem. Ecol. 40, 878–881. https://doi.org/10.1007/s10886-014-0467-4.

Averill, A.L., Couto, A.V., Andersen, J.C., Elkinton, J.S., 2021. Parasite prevalence may drive the biotic impoverishment of New England (USA) bumble bee communities. Insects 12, 941. https://doi.org/10.3390/insects12100941.

Baracchi, D., Brown, M.J.F., Chittka, L., 2015. Behavioral evidence for self-medication in bumblebees? F1000Research 4, 1–15. https://doi.org/10.12688/f1000research.6262.1.

Bärlocher, F., Graça, M.A.S., 2020. Chapter 18: total phenolics. In: Bärlocher, F., Graça, M.A.S., Gessner, M.O. (Eds.), Methods to Study Litter Decomposition: A Practical Guide. Springer International Publishing, Cham, Switzerland.

Barlow, S.E., Wright, G.A., Ma, C., Barberis, M., Farrell, I.W., Marr, E.C., Brankin, A., Pavlik, B.M., Stevenson, P.C., 2017. Distasteful nectar deters floral robbery. Curr. Biol. 27, 2552–2558. https://doi.org/10.1016/j.cub.2017.07.012 e3.

Barribeau, S.M., Sadd, B.M., du Plessis, L., Brown, M.J., Buechel, S.D., Cappelle, K., Carolan, J.C., Christiaens, O., Colgan, T.J., Erler, S., Evans, J., Helbing, S., Karaus, E., Lattorff, H.M.G., Marxer, M., Meeus, I., Näpflin, K., Niu, J., Schmid-Hempel, R., Smagghe, G., Waterhouse, R.M., Yu, N., Zdobnov, E.M., Schmid-Hempel, P., 2015. A depauperate immune repertoire precedes evolution of sociality in bees. Genome Biol. 16, 83. https://doi.org/10.1186/s13059-015-0628-y.

Bassolé, I.H.N., Juliani, H.R., 2012. Essential oils in combination and their antimicrobial properties. Molecules 17, 3989–4006. https://doi.org/10.3390/molecules17043989.

Berenbaum, M.R., Johnson, R.M., 2015. Xenobiotic detoxification pathways in honey bees. Curr. Opin. Insect Sci. 10, 51–58. https://doi.org/10.1016/j.cois.2015.03.005.

Bernays, E.A., Singer, M.S., 2005. Taste alteration and endoparasites. Nature 436, 476. https://doi.org/10.1038/436476a, 476.

Bernklau, E., Bjostad, L., Hogeboom, A., Carlisle, A., HS, A., 2019. Dietary phytochemicals, honey bee longevity and pathogen tolerance. Insects 10, 14. https://doi.org/10.3390/insects10010014.

Biller, O.M., Adler, L.S., Irwin, R.E., McAllister, C., Palmer-Young, E.C., 2015. Possible synergistic effects of thymol and nicotine against *Crithidia bombi* parasitism in bumble bees. PLoS One 10, e0144668. https://doi.org/10.1371/journal.pone.0144668.

Billiet, A., Meeus, I., Van Nieuwerburgh, F., Deforce, D., Wäckers, F., Smagghe, G., 2016. Impact of sugar syrup and pollen diet on the bacterial diversity in the gut of indoor-reared bumblebees (*Bombus terrestris*). Apidologie 47, 548–560. https://doi.org/10.1007/s13592-015-0399-1.

Blackmore, S., Wortley, A.H., Skvarla, J.J., Rowley, J.R., 2007. Pollen wall development in flowering plants. New Phytol. 174, 483–498. https://doi.org/10.1111/j.1469-8137.2007.02060.x.

Boncristiani, D.L., Tauber, J.P., Palmer-Young, E.C., Cao, L., Collins, W., Grubbs, K., Lopez, J.A., Meinhardt, L.W., Nguyen, V., Oh, S., Peterson, R.J., Zamora, H.,

Chen, Y., Evans, J.D., 2021. Impacts of diverse natural products on honey bee viral loads and health. Appl. Sci. 11, 10732. https://doi.org/10.3390/app112210732.
Boncristiani, H., Underwood, R., Schwarz, R., Evans, J.D., Pettis, J., vanEngelsdorp, D., 2012. Direct effect of acaricides on pathogen loads and gene expression levels in honey bees *Apis mellifera*. J. Insect Physiol. 58, 613–620. https://doi.org/10.1016/j.jinsphys.2011.12.011.
Boulanger, N., Bulet, P., Lowenberger, C., 2006. Antimicrobial peptides in the interactions between insects and flagellate parasites. Trends Parasitol. 22, 262–268. https://doi.org/10.1016/j.pt.2006.04.003.
Brochu, K.K., van Dyke, M.T., Milano, N.J., Petersen, J.D., McArt, S.H., Nault, B.A., Kessler, A., Danforth, B.N., 2020. Pollen defenses negatively impact foraging and fitness in a generalist bee (*Bombus impatiens*: apidae). Sci. Rep. 10, 3112. https://doi.org/10.1038/s41598-020-58274-2.
Brown, M.J.F., Loosli, R., Schmid-Hempel, P., 2000. Condition-dependent expression of virulence in a trypanosome infecting bumblebees. Oikos 91, 421–427. https://doi.org/10.1034/j.1600-0706.2000.910302.x.
Bulet, P., Hetru, C., Dimarcq, J.-L., Hoffmann, D., 1999. Antimicrobial peptides in insects; structure and function. Dev. Comp. Immunol., Invertebrate Immunity 23, 329–344. https://doi.org/10.1016/S0145-305X(99)00015-4.
Cameron, S.A., Lozier, J.D., Strange, J.P., Koch, J.B., Cordes, N., Solter, L.F., Griswold, T. L., 2011. Patterns of widespread decline in North American bumble bees. Proc. Natl. Acad. Sci. Unit. States Am. 108, 662–667. https://doi.org/10.1073/pnas.1014743108.
Camilo, C.J., Alves Nonato, C.D.F., Galvão-Rodrigues, F.F., Costa, W.D., Clemente, G.G., Sobreira Macedo, M.A.C., Galvão Rodrigues, F.F., Da Costa, J.G.M., 2017. Acaricidal activity of essential oils: a review. Trends Phytochem. Res. 1, 183–198.
Ceja-Navarro, J.A., Vega, F.E., Karaoz, U., Hao, Z., Jenkins, S., Lim, H.C., Kosina, P., Infante, F., Northen, T.R., Brodie, E.L., 2015. Gut microbiota mediate caffeine detoxification in the primary insect pest of coffee. Nat. Commun. 6, 7618. https://doi.org/10.1038/ncomms8618.
Chavan, P.S., Tupe, S.G., 2014. Antifungal activity and mechanism of action of carvacrol and thymol against vineyard and wine spoilage yeasts. Food Control 46, 115–120. https://doi.org/10.1016/j.foodcont.2014.05.007.
Chowański, S., Adamski, Z., Marciniak, P., Rosiński, G., Büyükgüzel, E., Büyükgüzel, K., Falabella, P., Scrano, L., Ventrella, E., Lelario, F., Bufo, S.A., 2016. A review of bioinsecticidal activity of solanaceae alkaloids. Toxins 8, 60. https://doi.org/10.3390/toxins8030060.
Cohen, H., Smith, G.P., Sardiñas, H., Zorn, J.F., McFrederick, Q.S., Woodard, S.H., Ponisio, L.C., 2021. Mass-flowering monoculture attracts bees, amplifying parasite prevalence. Proc. R. Soc. B Biol. Sci. 288, 20211369. https://doi.org/10.1098/rspb.2021.1369.
Collins, W., Lowen, N., Blake, D.J., 2019. Caffeic acid esters are effective bactericidal compounds against *Paenibacillus larvae* by altering intracellular oxidant and antioxidant levels. Biomolecules 9, 312. https://doi.org/10.3390/biom9080312.
Conroy, T.J., Palmer-Young, E.C., Irwin, R.E., Adler, L.S., 2016. Food limitation affects parasite load and survival of *Bombus impatiens* (Hymenoptera: apidae) infected with *Crithidia* (Trypanosomatida: trypanosomatidae). Environ. Entomol. 45, 1212–1219. https://doi.org/10.1093/ee/nvw099.
Costa, C., Lodesani, M., Maistrello, L., 2010. Effect of thymol and resveratrol administered with candy or syrup on the development of *Nosema ceranae* and on the longevity of honeybees (*Apis mellifera* L.) in laboratory conditions. Apidologie 41, 141–150. https://doi.org/10.1051/apido/2009070.
Couvillon, M.J., Al Toufailia, H., Butterfield, T.M., Schrell, F., Ratnieks, F.L.W., Schürch, R., 2015. Caffeinated forage tricks honeybees into increasing foraging and recruitment behaviors. Curr. Biol. 2815–2818. https://doi.org/10.1016/j.cub.2015.08.052.
de Miranda, J.R., Genersch, E., 2010. Deformed wing virus. J. Invertebr. Pathol. 103, S48–S61. https://doi.org/10.1016/j.jip.2009.06.012.
Di Pasquale, G., Salignon, M., Le Conte, Y., Belzunces, L.P., Decourtye, A., Kretzschmar, A., Suchail, S., Brunet, J.L., Alaux, C., 2013. Influence of pollen nutrition on honey bee health: do pollen quality and diversity matter? PLoS One 8, 1–13. https://doi.org/10.1371/journal.pone.0072016.
Dobson, H.E.M., Peng, Y.-S., 1997. Digestion of pollen components by larvae of the flower-specialist bee *Chelostoma florisomne* (hymenoptera: megachilidae). J. Insect Physiol. 43, 89–100. https://doi.org/10.1016/S0022-1910(96)00024-8.
Dolezal, A.G., Toth, A.L., 2018. Feedbacks between nutrition and disease in honey bee health. Curr. Opin. Insect Sci. 26, 114–119. https://doi.org/10.1016/j.cois.2018.02.006.
Domínguez, E., Mercado, J.A., Quesada, M.A., Heredia, A., 1998. Isolation of intact pollen exine using anhydrous hydrogen fluoride. Grana 37, 93–96. https://doi.org/10.1080/00173139809362649.
du Rand, E.E., Pirk, C.W.W., Nicolson, S.W., Apostolides, Z., 2017. The metabolic fate of nectar nicotine in worker honey bees. J. Insect Physiol. 98, 14–22. https://doi.org/10.1016/j.jinsphys.2016.10.017.
du Rand, E.E., Smit, S., Beukes, M., Apostolides, Z., Pirk, C.W.W., Nicolson, S.W., 2015. Detoxification mechanisms of honey bees (*Apis mellifera*) resulting in tolerance of dietary nicotine. Sci. Rep. 5, 11779. https://doi.org/10.1038/srep11779.
du Rand, E.E., Stutzer, C., Human, H., Pirk, C.W.W., Nicolson, S.W., 2020. Antibiotic treatment impairs protein digestion in the honeybee, *Apis mellifera*. Apidologie 51, 94–106. https://doi.org/10.1007/s13592-019-00718-4.
Ebeling, J., Knispel, H., Hertlein, G., Fünfhaus, A., Genersch, E., 2016. Biology of *Paenibacillus larvae*, a deadly pathogen of honey bee larvae. Appl. Microbiol. Biotechnol. 100, 7387–7395. https://doi.org/10.1007/s00253-016-7716-0.
Eckhardt, M., Haider, M., Dorn, S., Müller, A., 2014. Pollen mixing in pollen generalist solitary bees: a possible strategy to complement or mitigate unfavourable pollen properties? J. Anim. Ecol. 83, 588–597. https://doi.org/10.1111/1365-2656.12168.
Fan, T., Park, J.H., Pham, Q.A., Tan, E.-L., Mundargi, R.C., Potroz, M.G., Jung, H., Cho, N.-J., 2018. Extraction of cage-like sporopollenin exine capsules from dandelion pollen grains. Sci. Rep. 8, 6565. https://doi.org/10.1038/s41598-018-24336-9.
Figueroa, L.L., Blinder, M., Grincavitch, C., Jelinek, A., Mann, E.K., Merva, L.A., Metz, L. E., Zhao, A.Y., Irwin, R.E., McArt, S.H., Adler, L.S., 2019. Bee pathogen transmission dynamics: deposition, persistence and acquisition on flowers. Proc. R. Soc. B Biol. Sci. 286, 20190603. https://doi.org/10.1098/rspb.2019.0603.
Flesar, J., Havlik, J., Kloucek, P., Rada, V., Titera, D., Bednar, M., Stropnicky, M., Kokoska, L., 2010. In vitro growth-inhibitory effect of plant-derived extracts and compounds against *Paenibacillus larvae* and their acute oral toxicity to adult honey bees. Vet. Microbiol. 145, 129–133. https://doi.org/10.1016/j.vetmic.2010.03.018.
Folly, A.J., Koch, H., Farrell, I.W., Stevenson, P.C., Brown, M.J.F., 2021. Agri-environment scheme nectar chemistry can suppress the social epidemiology of parasites in an important pollinator. Proc. R. Soc. B Biol. Sci. 288, 20210363. https://doi.org/10.1098/rspb.2021.0363.
Folly, A.J., Stevenson, P.C., Brown, M.J.F., 2020. Age-related pharmacodynamics in a bumblebee–microsporidian system mirror similar patterns in vertebrates. J. Exp. Biol. 223, jeb217828. https://doi.org/10.1242/jeb.217828.
Fowler, A.E., Giacomini, J.J., Connon, S.J., Irwin, R.E., Adler, L.S., 2022. Sunflower pollen reduces a gut pathogen in the model bee species, *Bombus impatiens*, but has weaker effects in three wild congeners. Proc. R. Soc. B Biol. Sci. 289, 20211909. https://doi.org/10.1098/rspb.2021.1909.
Fowler, A.E., Stone, E.C., Irwin, R.E., Adler, L.S., 2020. Sunflower pollen reduces a gut pathogen in worker and queen but not male bumble bees. Ecol. Entomol. 45, 1318–1326. https://doi.org/10.1111/een.12915.
Geldert, C., Abdo, Z., Stewart, J.E., Arathi, H.S., 2021. Dietary supplementation with phytochemicals improves diversity and abundance of honey bee gut microbiota. J. Appl. Microbiol. 130, 1705–1720. https://doi.org/10.1111/jam.14897.
Getti, G.T.M., Aslam, S.N., Humber, D.P., Stevenson, P.C., Cheke, R.A., 2006. The effect of cicerfuran, an arylbenzofuran from *Cicer bijugum*, and related benzofurans and stilbenes on *Leishmania aethiopica, L. tropica* and *L. major*. Planta Med. 72, 907–911. https://doi.org/10.1055/s-2006-947187.
Gherman, B.I., Denner, A., Bobiș, O., Dezmirean, D.S., Mărghitaș, L.A., Schlüns, H., Moritz, R.F.A., Erler, S., 2014. Pathogen-associated self-medication behavior in the honeybee *Apis mellifera*. Behav. Ecol. Sociobiol. 68, 1777–1784. https://doi.org/10.1007/s00265-014-1786-8.
Giacomini, J.J., Adler, L.S., Reading, B.J., Irwin, R.E., 2021a. Differential bumble bee gene expression associated with pathogen infection and pollen diet. Prepr. Available Res. Sq. https://doi.org/10.21203/rs.3.rs-912647/v1.
Giacomini, J.J., Connon, S.J., Marulanda, D., Adler, L.S., Irwin, R.E., 2021b. The costs and benefits of sunflower pollen diet on bumble bee colony disease and health. Ecosphere 12, e03663. https://doi.org/10.1002/ecs2.3663.
Giacomini, J.J., Leslie, J., Tarpy, D.R., Palmer-Young, E.C., Irwin, R.E., Adler, L.S., 2018. Medicinal value of sunflower pollen against bee pathogens. Sci. Rep. 8, 14394. https://doi.org/10.1038/s41598-018-32681-y.
Giacomini, J.J., Moore, N., Adler, L.S., Irwin, R.E., 2022. Sunflower pollen induces rapid excretion in bumble bees: implications for host-pathogen interactions. J. Insect Physiol. https://doi.org/10.1016/j.jinsphys.2022.104356, 104356.
Gillespie and, J.P., Kanost, M.R., Trenczek, T., 1997. Biological mediators of insect immunity. Annu. Rev. Entomol. 42, 611–643. https://doi.org/10.1146/annurev.ento.42.1.611.
Goulson, D., Nicholls, E., Botías, C., Rotheray, E.L., 2015. Bee declines driven by combined stress from parasites, pesticides, and lack of flowers. Science 347, 1255957. https://doi.org/10.1126/science.1255957.
Graystock, P., Ng, W.H., Parks, K., Tripodi, A.D., Muñiz, P.A., Fersch, A.A., Myers, C.R., McFrederick, Q.S., McArt, S.H., 2020. Dominant bee species and floral abundance drive parasite temporal dynamics in plant-pollinator communities. Nat. Ecol. Evol. 1–10. https://doi.org/10.1038/s41559-020-1247-x.
Gutiérrez del Río, I., López Ibáñez, S., Magadán Corpas, P., Fernández Calleja, L., Pérez Valero, Á., Tuñón-Granda, M., Miguélez, E.M., Villar, C.J., Lombó, F., 2021. Terpenoids and polyphenols as natural antioxidant agents in food preservation. Antioxidants 10, 1264. https://doi.org/10.3390/antiox10081264.
Harris, E.V., Roode, J.C. de, Gerardo, N.M., 2019. Diet–microbiome–disease: investigating diet's influence on infectious disease resistance through alteration of the gut microbiome. PLoS Pathog. 15, e1007891 https://doi.org/10.1371/journal.ppat.1007891.
Heath, L.A.F., 1982. Chalk brood pathogens: a review. Bee World 63, 130–135. https://doi.org/10.1080/0005772X.1982.11097877.
Heil, M., Baumann, B., Andary, C., Linsenmair, E.K., McKey, D., 2002. Extraction and quantification of "condensed tannins" as a measure of plant anti-herbivore defence? Revisiting an old problem. Naturwissenschaften 89, 519–524. https://doi.org/10.1007/s00114-002-0366-3.
Hendriksma, H.P., Bain, J.A., Nguyen, N., Nieh, J.C., 2020. Nicotine does not reduce *Nosema ceranae* infection in honey bees. Insectes Sociaux 67, 249–259. https://doi.org/10.1007/s00040-020-00758-5.
Hsieh, E.M., Berenbaum, M.R., Dolezal, A.G., 2020. Ameliorative effects of phytochemical ingestion on viral infection in honey bees. Insects 11, 698. https://doi.org/10.3390/insects11100698.
Huang, W.-F., Solter, L.F., 2013. Comparative development and tissue tropism of *Nosema apis* and *Nosema ceranae*. J. Invertebr. Pathol. 113, 35–41. https://doi.org/10.1016/j.jip.2013.01.001.
Irwin, R.E., Cook, D., Richardson, L.L., Manson, J.S., Gardner, D.R., 2014. Secondary compounds in floral rewards of toxic rangeland plants: impacts on pollinators. J. Agric. Food Chem. 62, 7335–7344. https://doi.org/10.1021/jf500521w.

Jack, C.J., Uppala, S.S., Lucas, H.M., Sagili, R.R., 2016. Effects of pollen dilution on infection of *Nosema ceranae* in honey bees. J. Insect Physiol. 87, 12–19. https://doi.org/10.1016/j.jinsphys.2016.01.004.

Jeandet, P., Delaunois, B., Conreux, A., Donnez, D., Nuzzo, V., Cordelier, S., Clément, C., Courot, E., 2010. Biosynthesis, metabolism, molecular engineering, and biological functions of stilbene phytoalexins in plants. Biofactors 36, 331–341. https://doi.org/10.1002/biof.108.

Kaplan, I., Halitschke, R., Kessler, A., Sardanelli, S., Denno, R.F., 2008. Constitutive and induced defenses to herbivory in above- and belowground plant tissues. Ecology 89, 392–406. https://doi.org/10.1890/07-0471.1.

Kešnerová, L., Mars, R.A.T., Ellegaard, K.M., Troilo, M., Sauer, U., Engel, P., 2017. Disentangling metabolic functions of bacteria in the honey bee gut. PLoS Biol. 15, e2003467 https://doi.org/10.1371/journal.pbio.2003467.

Koch, H., Brown, M.J., Stevenson, P.C., 2017. The role of disease in bee foraging ecology. Curr. Opin. Insect Sci. 21, 60–67. https://doi.org/10.1016/j.cois.2017.05.008.

Koch, H., Schmid-Hempel, P., 2012. Gut microbiota instead of host genotype drive the specificity in the interaction of a natural host-parasite system. Ecol. Lett. 15, 1095–1103. https://doi.org/10.1111/j.1461-0248.2012.01831.x.

Koch, H., Schmid-Hempel, P., 2011. Socially transmitted gut microbiota protect bumble bees against an intestinal parasite. Proc. Natl. Acad. Sci. Unit. States Am. 108, 19288. https://doi.org/10.1073/pnas.1110474108, 19292.

Koch, H., Wellcome, V., Kendall-Smith, A., Thursfield, L., Farrell, I.W., Langat, M., Brown, M.J.F., Stevenson, P., 2022. Host and gut microbiome modulate the antiparasitic activity of nectar metabolites in a bumblebee pollinator. Philos. Trans. R. Soc. B Biol. Sci. https://doi.org/10.1098/rstb.2021.0162.

Koch, H., Woodward, J., Langat, M.K., Brown, M.J.F., Stevenson, P.C., 2019. Flagellum removal by a nectar metabolite inhibits infectivity of a bumblebee parasite. Curr. Biol. 29, 3494–3500. https://doi.org/10.1016/j.cub.2019.08.037 e5.

Kwong, W.K., Medina, L.A., Koch, H., Sing, K.-W., Soh, E.J.Y., Ascher, J.S., Jaffé, R., Moran, N.A., 2017. Dynamic microbiome evolution in social bees. Sci. Adv. 3, e1600513 https://doi.org/10.1126/sciadv.1600513.

Lipa, J.J., Triggiani, O., 1996. *Apicystis* gen nov and *Apicystis bombi* (liu, macfarlane & pengelly) comb nov (Protozoa: neogregarinida), a cosmopolitan parasite of *Bombus* and *Apis* (hymenoptera: apidae). Apidologie 27, 29–34. https://doi.org/10.1051/apido:19960104.

Little, T.J., Hultmark, D., Read, A.F., 2005. Invertebrate immunity and the limits of mechanistic immunology. Nat. Immunol. 6, 651–654. https://doi.org/10.1038/ni1219.

Liu, F., He, J., Fu, W., 2005. Highly controlled nest homeostasis of honey bees helps deactivate phenolics in nectar. Naturwissenschaften 92, 297–299. https://doi.org/10.1007/s00114-005-0629-x.

LoCascio, G.M., Aguirre, L., Irwin, R.E., Adler, L.S., 2019a. Pollen from multiple sunflower cultivars and species reduces a common bumblebee gut pathogen. R. Soc. Open Sci. 6, 190279. https://doi.org/10.1098/rsos.190279.

LoCascio, G.M., Pasquale, R., Amponsah, E., Irwin, R.E., Adler, L.S., 2019b. Effect of timing and exposure of sunflower pollen on a common gut pathogen of bumble bees. Ecol. Entomol. 44, 702–710. https://doi.org/10.1111/een.12751.

Loper, G.M., Standifer, L.N., Thompson, M.J., Gilliam, M., 1980. Biochemistry and microbiology of bee-collected almond (*Prunus dulcis*) pollen and bee bread. I. Fatty acids, sterols, vitamins and minerals. Apidologie 11, 63–73.

Lu, Y.-H., Wu, C.-P., Tang, C.-K., Lin, Y.-H., Maaroufi, H.O., Chuang, Y.-C., Wu, Y.-L., 2020. Identification of immune regulatory genes in *Apis mellifera* through caffeine treatment. Insects 11, 516. https://doi.org/10.3390/insects11080516.

Lunau, K., Piorek, V., Krohn, O., Pacini, E., 2015. Just spines—mechanical defense of malvaceous pollen against collection by corbiculate bees. Apidologie 46, 144–149. https://doi.org/10.1007/s13592-014-0310-5.

Madel, G., 1973. Zur Biologie des Hummelparasiten *Sphaerularia bombi* Dufour 1886 (Nematoda, Tylenchida). Bonn. Zool. Beitr. 24, 134–151.

Maes, P.W., Rodrigues, P.A.P., Oliver, R., Mott, B.M., Anderson, K.E., 2016. Diet-related gut bacterial dysbiosis correlates with impaired development, increased mortality and Nosema disease in the honeybee (*Apis mellifera*). Mol. Ecol. 25, 5439–5450. https://doi.org/10.1111/mec.13862.

Maistrello, L., Lodesani, M., Costa, C., Leonardi, F., Marani, G., Caldon, M., Mutinelli, F., Granato, A., 2008. Screening of natural compounds for the control of nosema disease in honeybees (*Apis mellifera*). Apidologie 39, 436–445. https://doi.org/10.1051/apido:2008022.

Manson, J.S., Otterstatter, M.C., Thomson, J.D., 2010. Consumption of a nectar alkaloid reduces pathogen load in bumble bees. Oecologia 162, 81–89. https://doi.org/10.1007/s00442-009-1431-9.

Mao, W., Schuler, M.A., Berenbaum, M.R., 2013. Honey constituents up-regulate detoxification and immunity genes in the western honey bee *Apis mellifera*. Proc. Natl. Acad. Sci. Unit. States Am. 110, 8842–8846. https://doi.org/10.1073/pnas.1303884110.

Mărgăoan, R., Topal, E., Balkanska, R., Yücel, B., Oravecz, T., Cornea-Cipcigan, M., Vodnar, D.C., 2021. Monofloral honeys as a potential source of natural antioxidants, minerals and medicine. Antioxidants 10, 1023. https://doi.org/10.3390/antiox10071023.

Marxer, M., Vollenweider, V., Schmid-Hempel, P., 2016. Insect antimicrobial peptides act synergistically to inhibit a trypanosome parasite. Philos. Trans. R. Soc. B Biol. Sci. 371, 20150302. https://doi.org/10.1098/rstb.2015.0302.

McNeil, D.J., McCormick, E., Heimann, A.C., Kammerer, M., Douglas, M.R., Goslee, S.C., Grozinger, C.M., Hines, H.M., 2020. Bumble bees in landscapes with abundant floral resources have lower pathogen loads. Sci. Rep. 10, 22306. https://doi.org/10.1038/s41598-020-78119-2.

Michaud, K.M., Irwin, R.E., Barber, N.A., Adler, L.S., 2019. Preinfection effects of nectar secondary compounds on a bumble bee gut pathogen. Environ. Entomol. 48, 685–690. https://doi.org/10.1093/ee/nvz018.

Mikulic-Petkovsek, M., Schmitzer, V., Jakopic, J., Cunja, V., Veberic, R., Munda, A., Stampar, F., 2013. Phenolic compounds as defence response of pepper fruits to *Colletotrichum coccodes*. Physiol. Mol. Plant Pathol. 84, 138–145. https://doi.org/10.1016/j.pmpp.2013.09.003.

Mockler, B.K., Kwong, W.K., Moran, N.A., Koch, H., 2018. Microbiome structure influences infection by the parasite *Crithidia bombi* in bumble bees. Appl. Environ. Microbiol. 84, e02335. https://doi.org/10.1128/AEM.02335-17, 17.

Moore, B.D., Andrew, R.L., Külheim, C., Foley, W.J., 2014. Explaining intraspecific diversity in plant secondary metabolites in an ecological context. New Phytol. 201, 733–750. https://doi.org/10.1111/nph.12526.

Motta, E.V.S., Raymann, K., Moran, N.A., 2018. Glyphosate perturbs the gut microbiota of honey bees. Proc. Natl. Acad. Sci. Unit. States Am. 115, 10305–10310. https://doi.org/10.1073/pnas.1803880115.

Naef, R., Jaquier, A., Velluz, A., Bachofen, B., 2004. From the linden flower to linden honey – volatile constituents of linden nectar, the extract of bee-stomach and ripe honey. Chem. Biodivers. 1, 1870–1879. https://doi.org/10.1002/cbdv.200490143.

Nolan, V.C., Harrison, J., Cox, J.A.G., 2019. Dissecting the antimicrobial composition of honey. Antibiotics 8, 251. https://doi.org/10.3390/antibiotics8040251.

Palmer-Young, E.C., Calhoun, A.C., Mirzayeva, A., Sadd, B.M., 2018. Effects of the floral phytochemical eugenol on parasite evolution and bumble bee infection and preference. Sci. Rep. 8, 2074. https://doi.org/10.1038/s41598-018-20369-2.

Palmer-Young, E.C., Farrell, I.W., Adler, L.S., Milano, N.J., Egan, P.A., Junker, R.R., Irwin, R.E., Stevenson, P.C., 2019. Chemistry of floral rewards: intra- and interspecific variability of nectar and pollen secondary metabolites across taxa. Ecol. Monogr. 89, e01335 https://doi.org/10.1002/ecm.1335.

Palmer-Young, E.C., Sadd, B.M., Adler, L.S., 2017a. Evolution of resistance to single and combined floral phytochemicals by a bumble bee parasite. J. Evol. Biol. 30, 300–312. https://doi.org/10.1111/jeb.13002.

Palmer-Young, E.C., Sadd, B.M., Irwin, R.E., Adler, L.S., 2017b. Synergistic effects of floral phytochemicals against a bumble bee parasite. Ecol. Evol. 7, 1836–1849. https://doi.org/10.1002/ece3.2794.

Palmer-Young, E.C., Sadd, B.M., Stevenson, P.C., Irwin, R.E., Adler, L.S., 2016. Bumble bee parasite strains vary in resistance to phytochemicals. Sci. Rep. 6, 37087. https://doi.org/10.1038/srep37087.

Palmer-Young, E.C., Tozkar, C.Ö., Schwarz, R.S., Chen, Y., Irwin, R.E., Adler, L.S., Evans, J.D., 2017c. Nectar and pollen phytochemicals stimulate honey bee (hymenoptera: apidae) immunity to viral infection. J. Econ. Entomol. 110, 1959. https://doi.org/10.1093/jee/tox193, 1972.

Pei, R., Zhou, F., Ji, B., Xu, J., 2009. Evaluation of combined antibacterial effects of eugenol, cinnamaldehyde, thymol, and carvacrol against *E. coli* with an improved method. J. Food Sci. 74, M379–M383. https://doi.org/10.1111/j.1750-3841.2009.01287.x.

Peng, Y.-S., Nasr, M.E., Marston, J.M., Fang, Y., 1985. The digestion of dandelion pollen by adult worker honeybees. Physiol. Entomol. 10, 75–82. https://doi.org/10.1111/j.1365-3032.1985.tb00021.x.

Piot, N., Meeus, I., Kleijn, D., Scheper, J., Linders, T., Smagghe, G., 2019. Establishment of wildflower fields in poor quality landscapes enhances micro-parasite prevalence in wild bumble bees. Oecologia 189, 149–158. https://doi.org/10.1007/s00442-018-4296-y.

Potts, S.G., Biesmeijer, J.C., Kremen, C., Neumann, P., Schweiger, O., Kunin, W.E., 2010. Global pollinator declines: trends, impacts and drivers. Trends Ecol. Evol. 25, 345–353. https://doi.org/10.1016/j.tree.2010.01.007.

Raymann, K., Bobay, L.-M., Moran, N.A., 2018. Antibiotics reduce genetic diversity of core species in the honeybee gut microbiome. Mol. Ecol. 27, 2057–2066. https://doi.org/10.1111/mec.14434.

Redondo-Blanco, S., Fernández, J., López-Ibáñez, S., Miguélez, E.M., Villar, C.J., Lombóba, F., 2019. Plant phytochemicals in food preservation: antifungal bioactivity: a review. J. Food Protect. 83, 163–171. https://doi.org/10.4315/0362-028X.JFP-19-163.

Richardson, L.L., Adler, L.S., Leonard, A.S., Andicoechea, J., Regan, K.H., Anthony, W.E., Manson, J.S., Irwin, R.E., 2015. Secondary metabolites in floral nectar reduce parasite infections in bumblebees. Proc. R. Soc. B 282, 20142471. https://doi.org/10.1098/rspb.2014.2471.

Richardson, L.L., Bowers, M.D., Irwin, R.E., 2016. Nectar chemistry mediates the behavior of parasitized bees: consequences for plant fitness. Ecology 97, 325–337. https://doi.org/10.1890/15-0263.1.

Rivest, S., Forrest, J.R.K., 2020. Defence compounds in pollen: why do they occur and how do they affect the ecology and evolution of bees? New Phytol. 225, 1053–1064. https://doi.org/10.1111/nph.16230.

Rodger, J.G., Bennett, J.M., Razanajatovo, M., Knight, T.M., van Kleunen, M., Ashman, T.-L., Steets, J.A., Hui, C., Arceo-Gómez, G., Burd, M., Burkle, L.A., Burns, J.H., Durka, W., Freitas, L., Kemp, J.E., Li, J., Pauw, A., Vamosi, J.C., Wolowski, M., Xia, J., Ellis, A.G., 2021. Widespread vulnerability of flowering plant seed production to pollinator declines. Sci. Adv. 7, eabd3524. https://doi.org/10.1126/sciadv.abd3524.

Rolff, J., Reynolds, S.E. (Eds.), 2009. Insect Infection and Immunity: Evolution, Ecology, and Mechanisms. Oxford University Press, Oxford, UK.

Rothchild, K.W., Adler, L.S., Irwin, R.E., Sadd, B.M., Stevenson, P.C., Palmer-Young, E.C., 2018. Effects of short-term exposure to naturally occurring thymol concentrations on transmission of a bumble bee parasite. Ecol. Entomol. 43, 567–577. https://doi.org/10.1111/een.12631.

Rothman, J.A., Leger, L., Kirkwood, J.S., McFrederick, Q.S., 2019. Cadmium and selenate exposure affects the honey bee microbiome and metabolome, and bee-associated

bacteria show potential for bioaccumulation. Appl. Environ. Microbiol. 85, e01411–e01419. https://doi.org/10.1128/AEM.01411-19.
Rubanov, A., Russell, K.A., Rothman, J.A., Nieh, J.C., McFrederick, Q.S., 2019. Intensity of *Nosema ceranae* infection is associated with specific honey bee gut bacteria and weakly associated with gut microbiome structure. Sci. Rep. 9, 3820. https://doi.org/10.1038/s41598-019-40347-6.
Sadd, B.M., 2011. Food-environment mediates the outcome of specific interactions between a bumblebee and its trypanosome parasite. Evolution 65, 2995–3001. https://doi.org/10.1111/j.1558-5646.2011.01345.x.
Samarghandian, S., Farkhondeh, T., Samini, F., 2017. Honey and health: a review of recent clinical research. Pharmacogn. Res. 9, 121–127. https://doi.org/10.4103/0974-8490.204647.
Schoonhoven, L.M., van Loon, J.J.A., Dicke, M., 2005. Plant chemistry: endless variety. In: Schoonhoven, L.M., van Loon, J.J.A., Dicke, M. (Eds.), Insect-Plant Biology. Oxford University Press, Oxford, UK.
Schwarz, R.S., Bauchan, G.R., Murphy, C.A., Ravoet, J., de Graaf, D.C., Evans, J.D., 2015. Characterization of two species of trypanosomatidae from the honey bee *Apis mellifera: Crithidia mellificae* langridge and McGhee, and *Lotmaria passim* n. gen., n. sp. J. Eukaryot. Microbiol. 62, 567–583. https://doi.org/10.1111/jeu.12209.
Scott-Brown, A.S., Gregory, T., Farrell, I.W., Stevenson, P.C., 2016. Leaf trichomes and foliar chemistry mediate defence against glasshouse thrips; *Heliothrips haemorrhoidalis* (Bouché) in *Rhododendron simsii*. Funct. Plant Biol. 43, 1170–1182. https://doi.org/10.1071/FP16045.
Singer, M.S., Mace, K.C., Bernays, E.A., 2009. Self-Medication as adaptive plasticity: increased ingestion of plant toxins by parasitized caterpillars. PLoS One 4, e4796. https://doi.org/10.1371/journal.pone.0004796.
Singh, D., 2014. Management of mite pests in honeybee colonies through botanicals. In: Singh, D. (Ed.), Advances in Plant Biopesticides. Springer India, New Delhi, pp. 271–277. https://doi.org/10.1007/978-81-322-2006-0_13.
Singh, S., Kaur, I., Kariyat, R., 2021. The multifunctional roles of polyphenols in plant-herbivore interactions. Int. J. Mol. Sci. 22, 1442. https://doi.org/10.3390/ijms22031442.
Singleton, V.L., Orthofer, R., Lamuela-Raventós, R.M., 1999. [14] Analysis of total phenols and other oxidation substrates and antioxidants by means of folin-ciocalteu reagent. In: Methods in Enzymology, Oxidants and Antioxidants Part A. Academic Press, pp. 152–178. https://doi.org/10.1016/S0076-6879(99)99017-1.
Singleton, V.L., Rossi, J.A., 1965. Colorimetry of total phenolics with phosphomolybdic-phosphotungstic acid reagents. Am. J. Enol. Vitic. 16, 144–158.
Sreevidya, N., Mehrotra, S., 2003. Spectrophotometric method for estimation of alkaloids precipitable with Dragendorff's reagent in plant materials. J. AOAC Int. 86, 1124–1127. https://doi.org/10.1093/jaoac/86.6.1124.
Steffan, S.A., Dharampal, P.S., Danforth, B.N., Gaines-Day, H.R., Takizawa, Y., Chikaraishi, Y., 2019. Omnivory in bees: elevated trophic positions among all major bee families. Am. Nat. 194, 414–421. https://doi.org/10.1086/704281.
Stevenson, P.C., 2020. For antagonists and mutualists: the paradox of insect toxic secondary metabolites in nectar and pollen. Phytochemistry Rev. 19, 603–614. https://doi.org/10.1007/s11101-019-09642-y.
Stevenson, P.C., Nicolson, S.W., Wright, G.A., 2017. Plant secondary metabolites in nectar: impacts on pollinators and ecological functions. Funct. Ecol. 31, 65–75. https://doi.org/10.1111/1365-2435.12761.
Stevenson, P.C., Veitch, N.C., 1998. A 2-arylbenzofuran from roots of *Cicer bijugum* associated with fusarium wilt resistance. Phytochemistry 48, 947–951. https://doi.org/10.1016/S0031-9422(97)00920-5.
Suárez-Cervera, M., Marquez, J., Bosch, J., Seoane-Camba, J., 1994. An ultrastructural study of pollen grains consumed by larvae of *osmia* bees (hymenoptera, megachilidae). Grana 33, 191–204. https://doi.org/10.1080/00173139409429000.
Szawarski, N., Saez, A., Domínguez, E., Dickson, R., De Matteis, Á., Eciolaza, C., Justel, M., Aliano, A., Solar, P., Bergara, I., Pons, C., Bolognesi, A., Carna, G., Garcia, W., Garcia, O., Eguaras, M., Lamattina, L., Maggi, M., Negri, P., 2019. Effect of abscisic acid (ABA) combined with two different beekeeping nutritional strategies to confront overwintering: studies on honey bees' population dynamics and nosemosis. Insects 10, 329. https://doi.org/10.3390/insects10100329.
Tadmor-Melamed, H., Markman, S., Arieli, A., Distl, M., Wink, M., Izhaki, I., 2004. Limited ability of Palestine Sunbirds *Nectarinia osea* to cope with pyridine alkaloids in nectar of Tree Tobacco *Nicotiana glauca*. Funct. Ecol. 18, 844–850. https://doi.org/10.1111/j.0269-8463.2004.00929.x.
Tauber, J.P., Tozkar, C.Ö., Schwarz, R.S., Lopez, D., Irwin, R.E., Adler, L.S., Evans, J.D., 2020. Colony-level effects of amygdalin on honeybees and their microbes. Insects 11, 783. https://doi.org/10.3390/insects11110783.
Thomson, J.D., Draguleasa, M.A., Tan, M.G., 2015. Flowers with caffeinated nectar receive more pollination. Arthropod-Plant Interact 1–7. https://doi.org/10.1007/s11829-014-9350-z.
Thorburn, L.P., Adler, L.S., Irwin, R.E., Palmer-Young, E.C., 2015. Variable Effects of Nicotine, Anabasine, and Their Interactions on Parasitized Bumble Bees. F1000Research 4. https://doi.org/10.12688/f1000research.6870.2.
Tiedeken, E.J., Egan, P.A., Stevenson, P.C., Wright, G.A., Brown, M.J.F., Power, E.F., Farrell, I., Matthews, S.M., Stout, J.C., 2016. Nectar chemistry modulates the impact of an invasive plant on native pollinators. Funct. Ecol. 30, 885–893. https://doi.org/10.1111/1365-2435.12588.
van den Bosch, T.J.M., Welte, C.U., 2017. Detoxifying symbionts in agriculturally important pest insects. Microb. Biotechnol. 10, 531–540. https://doi.org/10.1111/1751-7915.12483.
Vanbergen, A.J., Initiative, I.P., 2013. Threats to an ecosystem service: pressures on pollinators. Front. Ecol. Environ. 11, 251–259. https://doi.org/10.1890/120126.
Vanderplanck, M., Gilles, H., Nonclercq, D., Duez, P., Gerbaux, P., 2020. Asteraceae paradox: chemical and mechanical protection of *Taraxacum* pollen. Insects 11, 304. https://doi.org/10.3390/insects11050304.
Vanderplanck, M., Roger, N., Moerman, R., Ghisbain, G., Gérard, M., Popowski, D., Granica, S., Fournier, D., Meeus, I., Piot, N., Smagghe, G., Terrana, L., Michez, D., 2019. Bumble bee parasite prevalence but not genetic diversity impacted by the invasive plant *Impatiens glandulifera*. Ecosphere 10. https://doi.org/10.1002/ecs2.2804.
Vidkjær, N.H., Fomsgaard, I.S., Kryger, P., 2021. LC–MS/MS quantification reveals ample gut uptake and metabolization of dietary phytochemicals in honey bees (*Apis mellifera*). J. Agric. Food Chem. 69, 627–637. https://doi.org/10.1021/acs.jafc.0c03584.
Voulgari-Kokota, A., Steffan-Dewenter, I., Keller, A., 2020. Susceptibility of red mason bee larvae to bacterial threats due to microbiome exchange with imported pollen provisions. Insects 11, 373. https://doi.org/10.3390/insects11060373.
Wiese, N., Fischer, J., Heidler, J., Lewkowski, O., Degenhardt, J., Erler, S., 2018. The terpenes of leaves, pollen, and nectar of thyme (*Thymus vulgaris*) inhibit growth of bee disease-associated microbes. Sci. Rep. 8, 14634. https://doi.org/10.1038/s41598-018-32849-6.
Wright, G.A., Baker, D.D., Palmer, M.J., Stabler, D., Mustard, J.A., Power, E.F., Borland, A.M., Stevenson, P.C., 2013. Caffeine in floral nectar enhances a pollinator's memory of reward. Science 339, 1202–1204. https://doi.org/10.1126/science.1228806.
Wu, Y., Zheng, Y., Chen, Y., Chen, G., Zheng, H., Hu, F., 2020. *Apis cerana* gut microbiota contribute to host health though stimulating host immune system and strengthening host resistance to *Nosema ceranae*. R. Soc. Open Sci. 7, 192100. https://doi.org/10.1098/rsos.192100.
Xu, J., Zhou, F., Ji, B.-P., Pei, R.-S., Xu, N., 2008. The antibacterial mechanism of carvacrol and thymol against *Escherichia coli*. Lett. Appl. Microbiol. 47, 174–179. https://doi.org/10.1111/j.1472-765X.2008.02407.x.
Zattara, E.E., Aizen, M.A., 2021. Worldwide occurrence records suggest a global decline in bee species richness. One Earth 4, 114–123. https://doi.org/10.1016/j.oneear.2020.12.005.
Zheng, H., Nishida, A., Kwong, W.K., Koch, H., Engel, P., Steele, M.I., Moran, N.A., 2016. Metabolism of toxic sugars by strains of the bee gut symbiont *Gilliamella apicola*. mBio 7, e01326. https://doi.org/10.1128/mBio.01326-16, 16.