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Social-medication in bees: the line between individual and social regulation

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We use the term *social-medication* to describe the deliberate consumption or use of plant compounds by social insects that are detrimental to a pathogen or parasite at the colony level, result in increased inclusive fitness to the colony, and have potential costs either at the individual or colony level in the absence of parasite infection. These criteria for social-medication differ from those for self-medication in that inclusive fitness costs and benefits are distinguished from individual costs and benefits. The consumption of pollen and nectar may be considered a form of social immunity if they help fight infection, resulting in a demonstrated increase in colony health and survival. However, the dietary use of pollen and nectar *per se* is likely not a form of social-medication unless there is a detriment or cost to their consumption in the absence of parasite infection, such as when they contain phytochemicals that are toxic at certain doses. We provide examples among social bees (bumblebees, stingless bees and honey bees) in which the consumption or use of plant compounds have a demonstrated role in parasite defense and health of the colony. We indicate where more work is needed to distinguish between prophylactic and therapeutic effects of these compounds, and whether the effects are observed at the individual or colony level.

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Introduction

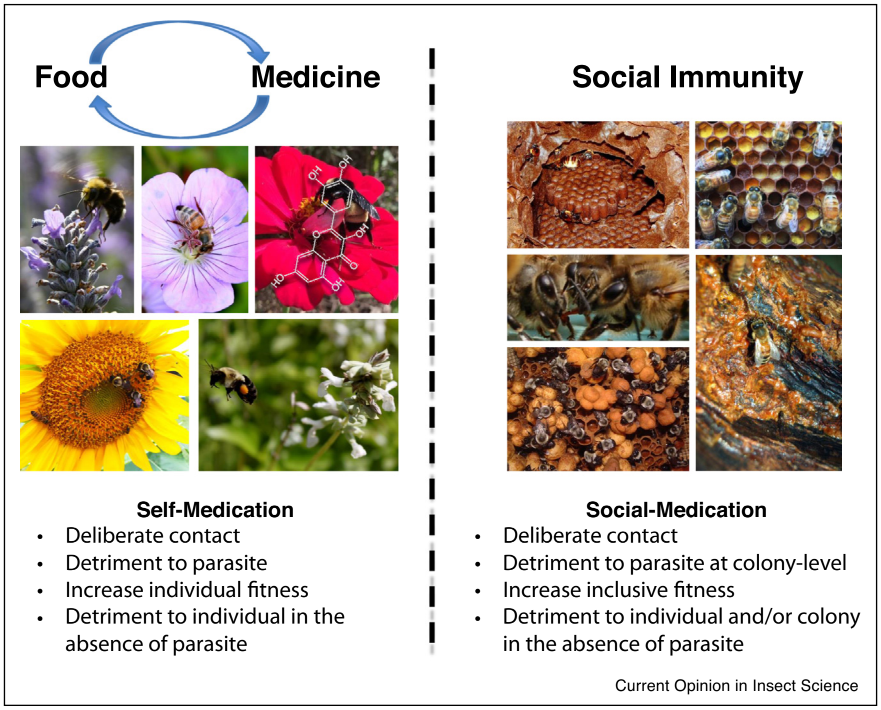
The concept of self-medication was defined by Clayton and Wolfe [1] as directed consumption or use of natural compounds by individual organisms to defend against parasites or pathogens. Clayton and Wolfe [1] outlined the first three criteria for self-medication, and the fourth was added later by Singer *et al.* [2]:

1 The [plant] substance must be deliberately contacted.
2 The substance must be detrimental to one or more parasites.
3 The detrimental effect on parasites increases host fitness.
4 The substance is detrimental to the host in the absence of parasites.

To date, examples of insects that meet all of these criteria are limited to four solitary insects (reviewed in Ref. [3]). Despite the limited number of examples, in recent years, researchers have applied the term self-medication to describe behaviors of social insects [4–8,9••,10,11]. However, examples of self-medication in social insects do not fully meet the above criteria because as de Roode *et al.* [12] point out, inclusive fitness benefits need to be considered. The host should be defined as the colony, not the individual, when calculating host fitness and detrimental effects. Criterion 4 is particularly difficult to test for social insects because substance use by the individual may be costly but beneficial to the colony overall (e.g. reduced disease transmission).

The goal of this review is to introduce the term *social-medication* and emphasize why it is important to make a distinction between self-medication and social-medication when describing the fitness costs and benefits to social insects for using plant compounds in parasite defense. We define social-medication as the deliberate consumption or use of plant compounds by social insects that are detrimental to a parasite or pathogen at the colony level, resulting in increased inclusive fitness benefits. As such, in the absence of parasite infection, potential costs of consuming or using plant (or other antimicrobial/antiparasitic) compounds may be either at the individual or colony level (Figure 1). Considering the value of inclusive fitness benefits and the concept of a social insect colony as a superorganism, costs should be assessed for both individuals and colonies. Individual costs may ultimately be absorbed by colony-level benefits or be restricted to so few individuals that the costs for the colony are negligible and, therefore, may falsely appear to not fulfill criterion 4. Further, social-medication is distinct from self-medication in that the host is the colony, not the individual. This distinction becomes significant, in particular, when

Figure 1



A comparison between self-medication and social-medication when plant compounds are consumed or used as defenses against parasites. Left side of dotted line: The list of criteria that must be met for a behavior to be considered self-medication, as reviewed in Abbot [3]. Right side of dotted line: The proposed list of criteria to be met for a behavior to be considered social-medication in social insect colonies. The criteria for social-medication differ from those for self-medication in that inclusive fitness costs and benefits are distinguished from individual costs and benefits. Social-medication is a form of social immunity if the plant compounds are shared among nestmates and help fight infection to increase colony health and survival.

considering the fact that social-medication may exist even when there is no evidence for self-medication. This review limits its discussion to honey bees, stingless bees and bumblebees.

The use of the term social-medication stems from the concept of social immunity. Social immunity describes the behaviors, organizational strategies and physiological mechanisms that colonies of ants, bees, wasps, and termites have evolved to defend against parasites (reviewed in Refs. [13••,14]). Social immunity provides a constructive framework for understanding how parasite and disease transmission can be reduced by collective actions and self-organization of individuals within the nest. These collective defenses can be either constitutive or induced [15], and are analogous to the actions of the immune system within an individual organism [16].

Interestingly, the *use* of plant compounds, such as antimicrobial resins, within the social insect nest architecture, has been considered a form of social immunity for multiple species [17–19], but the *consumption* of plant compounds by social insects has not [13••,14]. We suggest that the ingestion of plant compounds is a form of social immunity if the compounds are shared among nestmates and help fight infection to increase colony health and survival; that is, if the dietary choices of some individuals increase inclusive fitness at the colony level. This type of social immunity could also be considered social-medication if there are costs associated with the consumption of the plant compounds in the absence of infection. For all studies of social immunity and self-medication or social-medication, clarity is needed if the relative costs (i.e. detriments) and benefits to consuming or using plant compounds are at the individual or colony level.

We provide examples of consumption and use of plant compounds by social bees (e.g. bumblebees, stingless bees and honey bees) that have a demonstrated role in parasite defense and health of the colony, and when possible, delineate the extent of evidence for self-medication or for what we are calling social-medication. We structure this review following the quote of Hippocrates who said, referring to humans: “Let food be thy medicine and medicine be thy food,” and to include resin use by social bees we take the liberty of adding: “ . . . And do not limit thy medicine to food.”

Food as medicine: floral nutrition

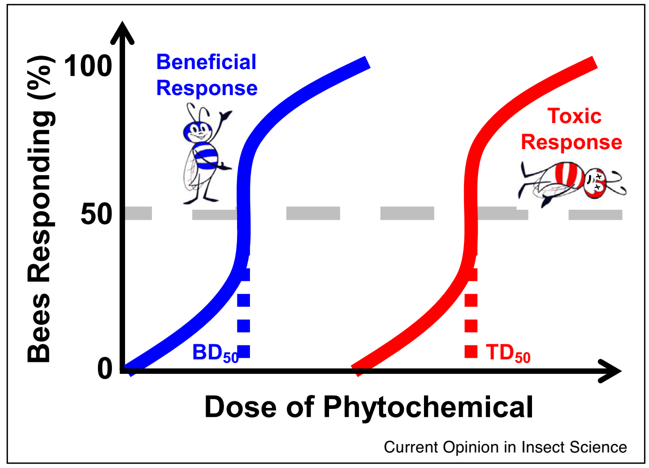
Pollen and nectar, and their associated microbial communities, are food for bees, providing nutrition and supporting immune and detoxification system function [20–24]. Individual foraging preferences by bees can impact colony-level pathogen load and colony survival (reviewed in Refs. [24,25]), and thus, nutrition *per se* can be a form of social immunity. However, in the absence of parasites, the collection and consumption of pollen and nectar is generally not detrimental to individual bees, or to the colony (except see Section 'Medicine as food: value added chemical compounds'), so nutrition *per se* is not a form of self-medication or social-medication based on criterion 4. Thus, dietary use of pollen improving tolerance of adult honey bees to infection by the microsporidian *Nosema ceranae* [26•,27], may be an example of social immunity if the benefits of individual bee's foraging decisions impact the health of the colony. Similarly for studies of bumblebees and other social bees, showing that individual preferences for pollen quality or quantity lead to reduced incidence of parasites and pathogens at the colony level would strengthen the argument that nutrition is a form social immunity [28–36].

In honey bees, pathogen infection may induce foragers from an infected colony to respond by selectively choosing nectar sources, or cause bees within the nest to choose among honey stores with specific anti-pathogenic properties as has been suggested [37,38]. The consumption of nectar and honey with varying antimicrobial properties to reduce pathogen load likely may have effects on social immunity at the colony level for all social bees. Only if the antimicrobial properties of nectar and honey have detrimental effects on individual bees or on a colony of bees in the absence of infection would their consumption be an example of self-medication or social-medication.

Medicine as food: value added chemical compounds

In addition to nutrition obtained from pollen and nectar, bees also benefit from phytochemicals in these resources. Phytochemicals are metabolites produced and used by plants for maintenance and defense. These bioactive compounds are likely non-nutritive and have inherent toxicity but can provide fitness benefits to bees when deliberately consumed as medicine. Adverse effects, especially to uninfected or otherwise healthy bees, are expected from doses that exceed therapeutic thresholds (Figure 2); thus, the deliberate consumption of phytochemicals could be a form of self-medication or social-medication. It is important to delineate the subtle difference between medicinal and dietary use of pollen and nectar. Dietary use connotes nutritional gain, whereas medicinal use assumes that bees commit to the forage and consumption of pollen and nectar specifically for their phytochemicals, for example, to reduce risk or counter an existing infection [2]. In fact, some studies report survival

Figure 2



Responses to different doses of a phytochemical. The BD_{50} is the dose where 50% of bees gain benefit from the phytochemical (e.g. parasite reduction). The TD_{50} is the dose where 50% of bees have an adverse response to the phytochemical (e.g. increased mortality). As the BD_{50} approaches the TD_{50}, benefits to the host from reduced parasitism are negated by toxic effects on host survival (Wellbee adapted from Centers for Disease Control and Prevention's Public Health Image #7224, CDC/Mary Hilpertshauser).

costs for uninfected bees after consuming natural levels of phytochemicals found in nectar [6,39•]. Therefore, medicinal benefits from phytochemical use should outweigh the costs of time and resources diverted from collecting dietary resources for nutrition, or supplanting existing individual immunity or social immunity strategies [40].

Several studies have explored fitness benefits from self-medication in social bees. For example, consumption of natural levels of phytochemicals can reduce parasite and pathogen load in experimentally infected bumblebees [[50••],41–44] (but see Ref. [45]) and honey bees [39•,46–48], even though chronic exposure could have implications for parasite resistance [49]. Although not plant-based, fungal exudates from polypore mushrooms can reduce viral titers of two common honey bee pathogens, Deformed wing virus (DWV) and Lake Sinai virus [50••]. Since honey bees have been observed foraging on mushrooms, this research raises questions about other compounds that bees utilize from their environment [11] and the effects of use on disease resistance or other health parameters (e.g. oxidative stress [40]) at the individual and colony levels. This is certainly relevant when thinking about how phytochemicals can also bolster detoxification. As a matter of practical significance, honey bee nests are frequently contaminated with pesticides [51] that may overwhelm the detoxification capacity of individual bees [52,53] and thus determining ways that bees are able to mitigate effects of pesticide exposure is of particular interest. Whether bees self-medicate or social-medicate in response to pervasive pesticide exposure, as they do to lessen the effects of parasites and pathogens, remains to be determined.

Changes in foraging preference by individual bees toward resources specifically for their bioactive compounds provides clear support for the role of self-medication in individual bee fitness. However, additional support is needed to ascertain whether self-medication can increase the fitness of the colony. Evidence of gains in inclusive fitness may be difficult to observe. It is safe to assume that infected individuals that self-medicate reduce the number of parasites or pathogens available for transfer to uninfected nestmates. Therefore, it may be possible to quantify indirect, colony-level benefits from these reductions, such as changes in adult population size or production of reproductives.

Storage of pollen and nectar by social bees also raises interesting questions about phytochemical usage within the nest across varying time scales. For example, do social bees maintain repositories of phytochemicals for communal use [6]? It is likely that nestmates, infected and healthy, are exposed not to single, but suites of phytochemicals with different modes of action and potencies that change with time and storage condition. These mixtures set the stage for complex interactions that result in synergistic [45,54] and antagonistic effects on parasite burden in individual bees [55], not to mention potential increased toxicity. Investigation of potential gains in colony fitness from the shared use of phytochemicals, either to prevent infection or inhibit its spread, and analysis of putative costs in the absence of infection, are needed to determine if these behaviors function as social-medication.

When medicine is not food: pharmacophory

Bees forage for other phytocompounds and incorporate them into their nest architecture; in these cases, the compounds are used but not consumed. Stingless bees collect plant resins, with some flowers even producing resin instead of nectar as an attractant. Resins stingless bees collect and mix with wax (and sometimes soil) for use in nest construction are known as geopropolis or cerumen. Honey bees, specifically *Apis mellifera*, collect chemically complex resins from various tree species and woody shrubs. They mix these resins with varying amounts of wax, and this admixture is referred to as propolis (recently reviewed in Ref. [56]). The role of propolis as a social immune defense in honey bees has been the subject of several recent studies [4,10,56,57,58••,59]. Propolis is typically deposited as a continuous, thin layer that covers the interior walls of feral colonies nesting in tree cavities but is patchily distributed in colonies managed in standard beekeeping equipment. Propolis has both direct and indirect effects on honey bee immunity and against various parasites and pathogens. The indirect benefits allow bees in a resin-rich nest environment to reduce investment in immune function (likely due to decreased colony microbial loads), which may have positive impacts on individual lifespan and colony productivity [56].

Since resin collection in honey bees is at least in part, constitutive, with a very small proportion of foragers consistently collecting resin, it has largely been viewed as a prophylactic mechanism of social immunity [15]. The question remains whether prophylactic behaviors can be considered as social-medication based on the criteria for self-medication. The argument for prophylactic resin collection, at least for honey bees, as a mechanism of social-medication is based on the idea that resin foraging is more costly at the individual level than foraging for nutritive items. While these costs have yet to be empirically tested, it does appear to take longer to forage for and unload resins in the hive compared to foraging for pollen and nectar [60•]. However, this does not seem to translate to costs at the colony level (e.g. brood and honey production), based on information from Africanized honey bees selected for increased propolis production [61,62]. The ability to conduct an empirical test to fulfill criterion 4 and document the cost of resin foraging when unchallenged is a major hurdle with respect to resin use. If resin foragers are responding to microbial loads (e.g. pathogenic, saprophytic, or symbiotic) in nest materials as well as those of nestmates, they are essentially constantly exposed and never performing the behavior in the absence of a challenge. It is possible that resin foragers differentially respond only to pathogenic microbes, and even in this case the persistence of at least low levels of pathogenic bacteria, fungi and viruses in honey stores and in the wax itself makes it unlikely that a honey bee colony is ever completely free of all pathogens. The more likely scenario is that a dose-dependency in colony-level microbes may be a factor in inducing resin collection. The mechanistic action behind resin foraging needs to be further explored to fully address this question.

One cue that does appear to induce resin collection is colony exposure to specific parasites and pathogens. Rates of resin foraging increase after colony infection with the fungal agent that causes chalkbrood in honey bee larvae (*Ascosphaera apis*), and propolis in the nest environment reduces chalkbrood infection [4]. This is the first evidence of social-medication in insects, where adults, without signs of infection, increased foraging of a non-nutritive substance to reduce infection of larval nestmates. Studies have also shown that resin foraging can be induced after colony infestation of the parasitic mite *Varroa destructor* [10] and infection with mite-vectored DWV [59]. Although results indicate that propolis-enriched colonies had reduced DWV titers [59], propolis does not appear to have a clear, direct effect against *V.*

destructor in the hive. While increased resin foraging in response to chalkbrood infection is a clear example of social-medication, it is possible that the increase seen with respect to *V. destructor* or DWV could be a form of both social-medication and self-medication. The regulation of this trait in response to parasite and pathogen challenge at the colony and individual levels remains unclear. For example, resin foraging does not increase indiscriminately to pathogen exposure, as it is not induced by exposure to the bacterial agent that causes American foulbrood in larvae (*Paenibacillus larvae*) [4]. Additionally, although the mechanism is unknown, a resin-rich environment can increase the medicative capacity of the larval diet, which constitutively has antimicrobial compounds that are either increased indirectly by nurse bees or enhanced by exposure to propolis volatiles [58••]. These examples highlight the complexity of the interaction between propolis in the nest environment, the physiology of adult bees and subsequently, larval susceptibility to disease.

Other species of bees and social insects, like ants, also collect resins for use in nest construction. While it appears that stingless bees use resins in part for recognition of conspecifics, they also appear to provide a role in defense. The role of resin in immunity and disease resistance of stingless bees is not well understood, but it is hypothesized that colonies that collect resins from diverse sources are more resistant to parasite and pathogen invasion [19]. In addition, at least for some species, resin collection increases during and after attack by ants [63]. Perhaps the concept of social-medication can be extended to external use of plant-derived compounds against predators if the predator is considered a colony-level parasite.

Species across the animal kingdom forage for antimicrobial compounds produced by other taxa, like plant resins or fungal mycelia. Since production of these compounds can be energetically demanding and evolutionary constrained based on an organism's physiology, this can be an effective strategy to access a large variety of chemical defenses. However, many social insects produce their own compounds with high levels of antimicrobial activity. In particular, the use of venom or other self-produced secretions by bees against the spread of disease deserves more attention. Recent evidence has shown that wood ants add ant-produced formic acid to tree resins deposited in the nest to increase its antimicrobial activity [64]. The case in wood ants appears to be a constitutive or prophylactic example of combining venom with foraged materials. Similarly in honey bees, venom has been found on wax comb and bee cuticle [65]. The function of this has not been fully tested, but it appears to also be prophylactic in the lens of both self-medication and social-medication. The clearest example of co-option of venom or poison gland secretions for disease resistance is from the garden ant *Lasius neglectus*. In this species, adult ants ingest a poisonous secretion from a gland, the acidopore. Adults then groom and spread this toxin on pupae infected with fungi [66]. While the uptake of this antifungal appears to be constitutive, the rate of grooming and dissemination of the poisonous secretion appears to be increased in the presence of pathogens [66]. In this way, this is a form of social-medication, despite the fact that the costs of conducting the behavior in the absence of pathogen exposure appear to be minimal at the individual level and potentially non-existent at the colony level. It remains to be determined if social bees use venom or other self-produced secretions in a similar way.

Conclusions

The concept of social immunity has greatly advanced the field of host–parasite interactions and mechanisms of disease resistance in social insects. We offer that the study of social immunity should include the consumption or use of plant compounds by social insects, if the compounds are shared among nestmates and help fight infection to increase colony health and survival. However, care must be taken when describing particular examples of collective pathogen defenses and dietary choices by social insects as *self-medication*. We propose instead the term *social-medication* to describe the deliberate consumption or use of plant compounds by social insects that are detrimental to a parasite or pathogen at the colony level, and result in increased inclusive fitness. The potential costs of social-medication at the individual versus colony level in the absence of parasite infection, the fourth criterion for social-medication, requires more attention.

Evidence that foraging preferences and the selection of in-hive dietary resources containing phytochemicals can be influenced by both individual infection status and colony-level exposure to parasites and pathogens raises the need to distinguish between self-medication and social-medication. Also, to fully understand the role of social-medication in impacting a colony's ability to resist parasites and pathogens, the mechanistic actions behind these behavioral decisions need to be explored. The consumption or use of plant compounds by a colony may be constitutive (i.e. prophylactic) but after a certain level of pathogen exposure, to individuals or colonies, these behavioral defenses can be induced and become therapeutic. It remains to be determined if these prophylactic and therapeutic behaviors have detrimental effects at the individual or colony level in the absence of infection. These costs may be difficult to ascertain, and in the case of honey bees where few individuals may partake in these behaviors, costs may only be expressed at the individual level and be swamped by the putative benefits at the colony level.

Conflict of interest statement

Nothing declared.

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