

Repellent properties of natural substances against *Dermanyssus gallinae*: review of knowledge and prospects for Integrated Pest Management

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Review

ABSTRACT

The poultry red mite *Dermanyssus gallinae* is a strict hematophagous parasite of birds, causing major health and economic problems in poultry farms worldwide. The use of plant-derived repellents against this pest could be an alternative control method as part of Integrated Pest Management strategies. In this review, the different types of repellents and the testing methods used to explore them in arthropods are synthesized. State-of-the-art knowledge on the repellent properties of natural plant-derived substances against *D. gallinae* is established. Studies reporting repellent properties exerted by plant-derived substances against *D. gallinae* are reviewed, and the level of discrimination between the different types of properties achieved by the experimental designs implemented is examined. Factors that may modulate repellent activity in arthropods are reviewed, and the available evidence for *D. gallinae* is highlighted. A framework is proposed for the rational use of knowledge from experiments for the implementation of Integrated Pest Management (IPM). In addition, to optimize the implementation of IPM strategies for *D. gallinae*, the current knowledge related to the risk of emergence of resistance to natural repellents is documented. This phenomenon has not been explored in *D. gallinae* to date, but resistance to several repellent substances has been reported in insects, with some cross-resistance between repellents and neurotoxic insecticides.

Keywords Poultry Red Mite; Integrated Pest Management; repellent; plant-derived substances; botanicals; resistance

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6	Framework on the integration of the repellent properties of substances of plant origin in Integrated Pest Management strategies for <i>D. gallinae</i>
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1 Introduction

The poultry red mite, *Dermanyssus gallinae* (De Geer, 1778), is a strictly hematophagous ectoparasitic mite frequently found in laying hen farms worldwide (Sparagano *et al.* 2014). *Dermanyssus gallinae* causes significant animal health problems (increased mortality, stress, weight loss, anemia and compromised immunity; Chauve 1998), with substantial economic impact within the egg industry (reduced egg laying percentage and egg quality). The estimated cost of treatment and production loss related to *D. gallinae* was estimated at 231 million euros per year for the egg industry in Europe in 2017 (Van Emous, 2017).

Control of *D. gallinae* is difficult due to its lifestyle. *Dermanyssus gallinae* needs blood meals to molt and lay eggs, but does not live on its host, as opposed to true ectoparasites, such as headlice. Instead it visits its host to take infrequent and relatively rapid blood meals, as do bedbugs or female mosquitoes. The rest of the time, individuals hide in interstices, where they form aggregates. This lifestyle corresponds to the category of “micropredators” as defined by Lafferty and Kuris (2002). Currently, the main treatments available against *D. gallinae* are synthetic neurotoxic acaricides, such as organophosphates, carbamates and pyrethroids, that are sprayed in the henhouse, this being the same application method used for alternative control products, including silica dusts and disinfectants. Premise sprays, however, are unable to effectively target mites that are secluded in interstices, particularly as many products lack prolonged residual toxicities in the dusty interiors of poultry facilities. The effectiveness of such treatments is therefore generally insufficient to deliver control, and high-level infestations of *D. gallinae* persist in farms regardless of spray operations. In addition, resistances to acaricides reinforce treatment failures. Delivery of acaricides systemically via host birds may be one option to improve treatment efficacy by ensuring better coverage of the full mite population. The oral administration of fluralaner (an isoxazoline) to hens as a systemic ectoparasiticide was recently approved, for example, and shows encouraging efficacy, at least for the time being (Brauneis *et al.* 2017).

Perhaps a more significant restriction for synthetic acaricides is that they can have a negative impact on both human health and the environment: indeed, some neurotoxic substances may have carcinogenic or reprotoxic effects, or impair mental health (Ansari, Moraiet and Ahmad 2014). Exposure routes may extend beyond the sector in which such treatments are used, where, for example, veterinary pesticides may be transferred to field crops through application of organic manures, such as those based on poultry litter (Motoyama *et al.* 2011; Kaczala and Blum 2016). The generally increasing societal demand for pesticide-free food thus makes the effective development of integrated pest management (IPM) against *D. gallinae* an urgent matter (Mul 2017).

IPM is already widely implemented in horticulture and field crops (Munk *et al.* 2020). However, current adoption of IPM strategies in animal production, and specifically in poultry farms, is limited by comparison and a major challenge for advanced sustainable egg production (Decru *et al.* 2020). IPM is based on three main principles: (1) the prevention and monitoring of pest populations and the application of treatments according to critical thresholds, (2) the promotion of alternative control methods (synthetic pesticides should be used as a last resort) and (3) the anticipation of resistance against alternative control means (Barzman *et al.* 2015).

In accordance with the above principle (2), a range of alternative *D. gallinae* control methods have been, or are being developed; these include: acaricidal substances of plant (e.g., certain essential oils) or mineral (e.g., silica powder) origin, repellent substances (mainly of

plant origin), electrified perches, vaccines, and heat treatment of the poultry unit between flocks during the empty period. Among these alternative treatments, substances derived from plants can be grouped into two distinct categories according to their use: they may be used for their acaricidal properties (toxic to the pest) or for their repellent properties (“unfriendly” to the pest). Whilst much work has already been directed to evaluating the potential of plant-based products as acaricides for *D. gallinae* (e.g. George *et al.* 2014), we choose here to focus on the less extensively considered role that such products could have as repellents for this pest.

Interfering in the chemical interactions between a pest and its host may form part of pest management by, (1) creating an odor barrier to prevent the pest from entering a space occupied by the host (e.g., repelling hematophagous arthropods from the host skin; Brown and Hebert 1997), or (2) interfering with pest-host interactions to prevent pests from developing under favourable conditions on the target host (e.g., by intercropping repellent companion plants between the cultivated plants to discourage herbivorous insects from landing on the latter; Ben Issa *et al.* 2017). The use of repellent secondary metabolites of plants may be an interesting alternative to synthetic acaricides against *D. gallinae*. Not only do plant-derived products have low environmental persistence and natural degradation pathways, but also repellents are typically based on the application of low concentrations. These characteristics make plant-based repellents interesting tools for mitigating the impact of pest management in agriculture on biodiversity, keeping in mind that concentration is relative and that some plants can be highly toxic at low concentrations. However, the effective application of these properties for pest control in crop production requires an improved understanding of the mechanisms involved (Deletre *et al.* 2016). This understanding is lagging even further behind in the context of pest control in livestock production; thus, there is a need to refine our understanding of the repellent properties of plant products against *D. gallinae*.

Deletre *et al.* (2016) described the typical two-step sequence for host location in phytophagous insects. Given the similarities between most plant-phytophagous insect and host-“micropredator” relationships, we consider here this two-step sequence can also be applied to hematophagous arthropods in the “micropredator” category. The first step is the “choice” of host and consists of searching for and recognizing the host by means of olfactory and/or visual clues/stimuli. This choice is made at a distance from the host. In the case of hematophagous micropredators, sensory systems other than olfactory systems in the strict sense or visual systems can also be involved in this stage (detection of gases such as CO₂ and detection of heat sources). The second step is the “selection” of the host, which consists of accepting the host and, in some cases, selecting a suitable feeding area on the host body on the basis of contact chemoreception (or “taste”). This second step takes place at, or after, the time of contact.

Dethier *et al.* (1960) defines a repellent as “any stimulus that elicits an avoiding reaction”. Miller *et al.* (2009) redefine the term repellent as “a chemical causing a responder to make movements oriented away from the stimulus source”. Deletre *et al.* (2016) suggest a categorization of repellents based on the behavioral response of insect pests to these products with regard to the targeted step. Here, repellents are classified into five categories: true repellent, odor masking, visual masking, irritant (contact irritancy), and antifeedant. An oriented movement of the insect away from the source of the odor, without direct contact with the product, characterizes a “true repellent”. Odor and visual masking disturbs host localization or decreases host attractiveness. Otherwise, if the response occurs after direct contact with the product, the repellent is an “irritant”, with an “antifeedant” disturbing feeding activity after ingestion. “True repellents”, “odor masking” and “visual masking”, target the “choice” step, while “irritants” and “antifeedants” target the “selection” step.

In this article, we provide an overview of the available knowledge on the different types of plant-derived repellents against *D. gallinae* as alternative IPM products that could help to reduce the use of synthetic treatments (see principle (2) of IPM above), taking into account possible resistance development against them (see principle (3) above). To clearly delimit the scope of the review, we first present the distinction between repellency and toxicity, placing these properties in a framework of evolutionary history, then in the context of the control of

D. gallinae in poultry. Second, we describe the methodologies that are or have been used to explore the different types of repellency against various arthropods. Then, a synthesis of the studies available to date on the repellency of natural plant-derived substances to *D. gallinae* is provided, summarizing methods, types of repellency tested, general results obtained so far in different families of plants according to factors that may influence the repellent effect of these substances. Later, we discuss the gaps and needs, in terms of experiments, to progress the implementation of plant-derived repellents in IPM. Finally, any selection pressure exerted by humans in pest management is susceptible to encountering resistance in the pest, which may strongly impair the sustainability of the treatment efficacy. Therefore, we also review the current knowledge about resistance to repellents.

2 Repellent and toxic properties of plant-derived substances: two evolutionarily linked but distinct features

Plants produce many volatile secondary metabolites, the ancestral function of which seems to be defense against herbivorous arthropods (Harrewijn *et al.* 1995, Pichersky and Gershenzon 2002). Herbivore-induced volatile compounds that attract the natural enemies of herbivores occur in situations of indirect defence by plants (see McCormick *et al.* 2012). In the context of direct plant defence, the repellent properties of the emitted compounds may deter the herbivore from exposing itself, or its endosymbionts, to directly toxic effects of these chemicals (Harrewijn *et al.* 1995), with repellency against hematophagous insects suggested to be an evolutionary relic passed from ancestors who fed on plants (Maia and Moore 2011). The fact that several substances of plant origin have both acaricidal and repellent properties is consistent with the extension of this hypothesis to hematophagous arachnids (e.g., thyme and oregano essential oils against *D. gallinae* (George *et al.* 2009b, Nechita *et al.* 2015) and thymol and carvacrol against the tick *Ixodes ricinus*, (Tabari *et al.* 2017b)). In most cases, higher concentrations are needed to achieve acaricidal/insecticidal effects than to achieve repellent effects (e.g., 3 times with thymol and essential oil of seeds of *Trachyspermum ammi* against a mosquito in Pandey *et al.* 2009, up to 5 times with tea tree oil of *Melaleuca alternifolia* against fly larvae in Callander and James 2012 and > 20 times with α -terpineol against a beetle in Garcia *et al.* 2005). Therefore, deployment of these substances as repellents is likely to have reduced animal health and environmental impacts compared to acaricidal uses. To the best of our knowledge, no plant-derived substances are currently authorized for administration in feed to hens at doses sufficient to have acaricidal properties against *D. gallinae* via the blood meal, while some are commonly used for administration in feed as repellents (see El Adouzi *et al.* 2019). Plant substances used for their acaricidal properties against *D. gallinae* can be applied by spraying (e.g., neem oil, Camarda *et al.* 2018) and encounter the same disadvantages as sprayed synthetic acaricides (see above). In general, because hematophagous arthropods in the “micropredator” category need to locate their host remotely (step 1 above), the application of essential oils as an acaricide or insecticide appears to be more appropriate for the control of “permanent” parasites than for hematophagous arthropods that do not live permanently on the host (Ellse and Wall 2014). Plant-derived or synthetic acaricidal substances can also be applied in a more targeted manner, by impregnation of *D. gallinae* traps, provided that repellency is limited (e.g., Lundh *et al.* 2005). The fundamental differences between the two uses mean that the detailed analyses of these modes of action require different skills, focusing on toxicity for acaricidal uses or on the response to olfactory stimuli for repellent uses. Here, only the latter will be explored.

3 Methodology of analysis of the different categories of repellency

The activity of a repellent is typically measured by behavioral tests. Most of them offer the arthropod a choice between a neutral element (control) and the substance to be tested. To determine the type of repellency generated by a substance on a given animal, it is necessary to set up a discriminating experimentation protocol. To test true repellency, bioassays must prevent any contact between the insect and the stimulus itself (Deletre *et al.* 2016). Olfactometric test systems based on two controlled air flows, one of which is loaded with volatile test compounds and the other is pure (control), are generally set up to offer a binary choice to the animal under consideration (e.g., with *D. gallinae*: Birkett *et al.* 2008; Georges *et al.* 2009b; Dehghani-Samani *et al.* 2015; Tabari *et al.* 2017a; El Adouzi *et al.* 2019). The shape of the part in which the air is circulated and into which the animal is introduced is very important. Y-tubes are typically employed here, and are valuable devices for carrying out choice tests with attractants, especially when comparing a control (pure air) to the odor being tested. Indeed, they offer the animal introduced into the central branch a gradient of the tested compound or blend (Bock and Cardew, 2008), which guides it to the interesting source. Conversely, they are not very suitable for repellency testing because the animal is immediately confronted with the repellent volatile compounds in the central branch and may turn away before entering the area of choice (the crossroads between the two upper branches). This can result in many animals not making a choice, thus leading to unclear results (Grieco *et al.* 2005; Deletre *et al.* 2016). To overcome this issue, T-shaped mazes with an entrance just in the middle of the upper bar allows the offer of a strictly binary choice for the animal (see El Adouzi *et al.* 2019). Similarly, four-branch olfactometers allow the animal to be inserted at a central point to ensure that a choice is made (insertion at the junction of the four arms). The probabilities of visits to each branch are equal (1/4 each). In general, one branch delivers the odor of the repellent tested, and the other branches serve as controls (Bruce *et al.* 2015; Deletre *et al.* 2016). The animal's movements and positions within the four arms of the olfactometer are recorded over set periods to study its behavior in the presence of the substance tested. To specifically test irritancy, the experimental device must ensure contact between the animal and the tested product (Deletre *et al.* 2016). For example, Martin *et al.* (2013) tested the irritancy of α -cypermethrin on the aphid, *Myzus persicae* by comparing the movement (speed, mobility, distance traveled) of single aphids in constant contact with treated vs untreated nets.

When there is no attempt to differentiate the type of repellent properties, materials such as filter paper and traps, whether or not impregnated with the substance being tested, can be placed at specific locations in any kind of arena, including 4-branch structures or any other setup where arthropods are introduced, and the distribution of arthropods recorded after a given interval. Obtained results provide a rough idea of the activity of the test substance (repellent or not), but a more detailed understanding of the mode of action may be necessary depending on the operational objectives: if one wants to keep the mite away from the hen, for example, it is probably more appropriate to use a true repellent than an irritant. The latter not only risks having a narrower range of action (and therefore affecting fewer individuals at the same time), but also has little chance of being emitted homogeneously over the whole body of the hen at the scale of the mite. Irritants may nevertheless have a role in *D. gallinae* IPM, for example to prevent mites from accessing specific areas (e.g., the base of a perch); in such instances they may even perform better than true repellents acting on contact and often not volatilizing as quickly. In short, the experimental system determines the type(s) of repellency that can be measured, and it is therefore crucial to select methodologies that align well to end uses and defined research questions.

Finally, the number of mites used in each test is also an important parameter to take into account, especially since *D. gallinae* is known to emit aggregation pheromones (Entrekin and Oliver 1982; Koenraadt and Dickens 2010). Interactions between the pheromones and potentially repellent volatile compounds may confound results when testing on groups of

mites. Testing mites individually (and each in a clean, pheromone-free device) overcomes this issue and guarantees that only the test substance influences the data. Conversely, testing individuals in groups allows the effect of the test substance to be reported in the presence of possible interactions with aggregation pheromones, as they would occur in the field. However, in this case, the amount and distribution of the pheromone are not controlled, which is likely to introduce unwanted “noise”. Ideally, testing mites both individually and in groups could be recommended to allow evaluations of these interactions and provide data on what may be happening with mite aggregates vs. single mites in transit on a farm.

4 Repellents of plant origin against *D. gallinae*

4.1 Plant parts and plant extracts

Available studies on plant-derived repellents against *D. gallinae* may be split into two groups (Table 1): studies that focused on true repellency alone by implementing bioassays without any direct contact with the stimulus, and studies that examined repellency in general without differentiating the category by implementing bioassays that neither preclude nor require contact. We did not find any studies reporting odor masking or antifeedant properties from plant-derived substances against *D. gallinae* (and visual masking cannot work with this mite, as it is blind and can only detect variations in light, not shapes).

Plant-derived repellents against *D. gallinae* can be derived from different types of substances, including resins, leaf powder, plant powder, methanolic extracts and fractions of plants or essential oils (Table 1). To date, plant species from at least 15 different botanical families have been tested, 13 of which were found to include plants with substances repellent to *D. gallinae*. The resin of *Commiphora holtziana* spp. *holtziana* (gum haggard), extracts of *Conocarpus erectus*, methanolic extracts and fractions of *Cnidium officinale* (Kim *et al.* 2018), and several essential oils, including thyme (*Thymus vulgaris*), have shown significant repellency during *in vitro* tests (Table 1). It is worth noting that some of these plant-derived substances are also known for their toxic properties to *D. gallinae* (*C. officinale*, Kim *et al.* 2004; manuka (*Leptospermum scoparium*), thyme (*T. vulgaris*), clove bud (*Syzygium aromaticum* = *Eugenia caryophyllata*), George *et al.* 2010). Some may also negatively affect the health of vertebrates, including hens and man (Bakkali *et al.* 2008, George *et al.* 2014, Lee 2018). As previously noted, however, repellent activity of these substances is typically realized at lower concentrations than toxicity, where these can be expected to be relatively safe to non-target organisms.

Chemical compounds from the same plant species can vary in quality and quantity between batches studied (Thompson *et al.* 2003; George *et al.* 2009a, Ben Jemâa *et al.* 2012; Dardouri *et al.* 2019). Tabari *et al.* (2017a) analyzed the composition of *Artemisia sieberi* essential oil used in their repellency experiments on *D. gallinae*. It was mainly composed of α -thujone (31.5%), in contrast to other studies previously carried out on this essential oil, where camphor was reported as the main compound (Weyerstahl *et al.* 1993; Sefidkon *et al.* 2002; Negahban *et al.* 2007). Intraspecific variation in the chemical composition of essential oil has been reported for other plants (e.g., *T. vulgaris*, Piccaglia and Marotti 1993; McGimpsey *et al.* 1994; Porte and Godoy 2008; Imelouane *et al.* 2009). It varies according to several parameters, including environmental conditions (Piccaglia *et al.* 1993) and the season of harvest (McGimpsey *et al.* 1994). Georges *et al.* (2009) reported considerable variation in lethal exposure time values for essential oil of the same plant species in *D. gallinae*. They suggest that these variations could be due to a difference in the chemical composition (and thus in the acaricidal activity) of this essential oil. Different effects from those listed in Table 1 could therefore be exerted depending on the chemotype of the plant used, information that is generally not indicated in the available studies on this mite.

Table 1 Summary of studies published prior to August 2020 on plant-derived repellents against *Dermanyssus gallinae*. In the category of repellency tested, ‘true repellents’ have been defined where mites could not contact test substances, and ‘undifferentiated’ has been used as a category where contact between mites and the repellent was possible during experiments, but not exclusively defined (such that no distinction was possible between true repellency and irritancy). The different response variable are: (a) number of mites standing in different areas of the arena (or in cardboard traps or on the host) at fixed time intervals, (b) active choice of a specific area by single individuals (dynamic behavior), (c) time for a mite to reach an area of the test arena within one time interval, and (d) percentage of area avoided by the mites during the experiment (movements recorded using a camera).

Category of repellency tested	Choice proposal method	Response variable	Mite test mode	Plant family	Botanical taxon	Tested substance	Results	References
True repellent	Four-way olfactometer	a	Single adult individual	Bursaceae	<i>Commiphora holziana</i> spp. <i>holziana</i>	Gum (extracts in different kinds of solvents)	Repellency detected depending on the kind of extract and the mite's physiological status (fed/starved)	Birkett et al. 2008
		a	Single adult individual	Bursaceae	<i>Commiphora myrrha</i>	Gum (extracts in different kinds of solvents)	No repellency detected	Birkett et al. 2008
	T-tubes	a	Single individual	Apiaceae	<i>Cnidium officinal</i>	Methanolic extract and (Z)-ligustilide	Repellency detected of methanolic extract and (Z)-ligustilide	Kim et al. 2018
		a	Group (10 to 25 starved females)	Lauraceae	Cinnamon bark (unspecified specie)	Essential oil and volatile organic compounds	Repellency detected	Lee et al. 2019
			Group (10 to 25 starved females)	Myrtaceae	Clove (unspecified specie)	Essential oil of bud and volatile organic compounds	Repellency detected of essential oil	Lee et al. 2019
		a				Essential oil of bud and volatile organic compounds	Variation in the repellency of eugenol and eugenol acetate depending on exposure duration	
		b	Single individual	Mix Myrtaceae and Poaceae	<i>Syzygium aromaticum</i> and <i>Cymbopogon nardus</i>	Volatile organic compounds	Repellency detected of eugenol, geraniol, trans-caryophyllene, geranyl acetate and linalool	El Adouzi et al. 2019
			Group (50 adults)	Asteraceae	<i>Artemisia sieberi</i>	Essential oil	Repellency detected	Tabari, Youssefi and Benelli 2017
	Y-tubes	a	Group (ca. 40 females)	Apiaceae	<i>Carum carvi</i>	Essential oil	Repellency detected	George et al. 2009b
		a	Group (ca. 40 females)	Cupressaceae	<i>Juniperus communis</i>	Essential oil	Repellency detected	George et al. 2009b
		a	Group (ca. 40 females)	Lamiaceae	<i>Mentha spicata</i>	Essential oil	Repellency detected	George et al. 2009b
		a	Group (ca. 40 females)	Lamiaceae	<i>Thymus vulgaris</i>	Essential oil	Repellency detected	George et al. 2009b
		a	Group (50 mites)	Lamiaceae	Unspecified species	Volatile organic compounds	Repellency detected of carvacrol and thymol	Masoumi et al. 2016
		a	Group (50 mites)	Myrtaceae	<i>Eucalyptus globulus</i>	Essential oil	Repellency detected	Dehghani-Samani et al. 2015
		a	Group (ca. 40 females)	Myrtaceae	<i>Leptospermum scoparium</i>	Essential oil	Repellency detected	George et al. 2009b
		c	Group (5 mites)	Myrtaceae	<i>Myrcia elongata</i>	Essential oil	Repellency detected for 10% concentration	Samana et al. 2018
							No repellency detected for 1% and 5% concentrations	
		a	Group (ca. 40 females)	Piperaceae	<i>Piper nigrum</i>	Essential oil	Repellency detected	George et al. 2009b
Undifferentiated	2 pieces of impregnated filter paper in a Petri dish	a	Group (5 adults females)	Anacardiaceae	<i>Pistacia atlantica</i>	Leaf powder	Repellency detected	Rajabpour, Mashhadi and Ghorbani 2018
		a	Group (5 adults females)	Combretaceae	<i>Conocarpus erectus</i>	Leaf powder	Repellency detected	Rajabpour, Mashhadi and Ghorbani 2018
		a	Group (5 adults females)	Portulacaceae	<i>Portulaca oleracea</i>	Leaf powder	No repellency detected	Rajabpour, Mashhadi and Ghorbani 2018
	2 pieces of impregnated filter paper placed in a glass facility	d	Single individual	Apiaceae	Coriander (unspecified species)	Essential oil	Repellency detected	Nechita et al. 2015
		d	Single individual	Cupressaceae	Juniper (unspecified species)	Essential oil	Repellency detected	Nechita et al. 2015
		d	Single individual	Lamiaceae	Basil (unspecified species)	Essential oil	Repellency detected	Nechita et al. 2015
		d	Single individual	Lamiaceae	Oregano (unspecified species)	Essential oil	Repellency detected	Nechita et al. 2015
		d	Single individual	Lamiaceae	Thyme (unspecified species)	Essential oil	Repellency detected	Nechita et al. 2015
		d	Single individual	Myrtaceae	Eucalyptus (unspecified species)	Essential oil	Repellency detected	Nechita et al. 2015
		d	Single individual	Rutaceae	Lemon (unspecified species)	Essential oil	Repellency detected	Nechita et al. 2015
		d	Single individual	Lamiaceae	Lavender (unspecified species)	Essential oil	Repellency detected	Nechita et al. 2015
	Cardboard traps impregnated by chemotype A and/or	d	Single individual	Lamiaceae	Mint (unspecified species)	Essential oil	Repellency detected	Nechita et al. 2015
		d	Single individual	Pinaceae	Fir tree (unspecified species)	Essential oil	Repellency detected	Nechita et al. 2015
		a	Group (<i>in vivo</i> test)	Lamiaceae	<i>Nepeta cataria</i>	Essential oil	Repellency detected (no difference detected between chemotypes)	Birkett et al. 2011
		a	Group (<i>in vivo</i> test)	Mix Apiaceae, Fabaceae and Lauraceae	<i>Foeniculum vulgare</i> , <i>Sophora flavescens</i> , <i>Cinnamomum cassia</i> and <i>Glycyrrhiza glabra</i>	Plant powder	Repellency detected	Chae et al. 2019

4.2 Individual chemical compounds

In view of the intraspecific variation in the composition of volatile compounds for the same species of plant, the repellent effects of individual chemical compounds of plant origin also deserve to be studied to characterize more precisely the substances responsible for repellency. El Adouzi *et al.* (2019) have studied the repellent activity of six plant-derived compounds emitted by hens as part of their odor after they ingested a plant-based in-feed supplement. Six volatile organic compounds were tested using T-shaped mazes and controlled air flows, five of which were found to be emitted by the supplement itself, as well as by the supplemented hens (namely, eugenol, geraniol, trans-caryophyllene, geranyl acetate and linalool), and one of which was found to be absent from the supplement, but emitted by supplemented hens (α -terpineol), likely as a result of metabolization. The first five were shown to be true repellents against *D. gallinae* (El Adouzi *et al.* 2019).

Masoumi *et al.* (2016) studied the repellent effects of carvacrol and thymol (Table 1). Carvacrol is a monoterpenoid phenol frequently found in Labiatae-based essential oils (Jayakumar *et al.* 2012) and is known for its acaricidal properties (Ahn *et al.* 1998). Thymol is a monoterpene found in essential oil of thyme (Piccaglia and Marotti 1993; McGimpsey *et al.* 1994; Porte and Godoy 2008). Both carvacrol and thymol have been shown to be true repellents against *D. gallinae*.

In short, the repellent properties of plants are not necessarily homogeneous within the plant itself and may vary according to the plant part or method of extraction considered. Therefore, a repellent property cannot be generalized to an entire plant for application to pest control.

5 Factors modulating the repellent activity of natural substances against *D. gallinae*

5.1 Physiological status of mites

The mite's physiological status may have an impact on the host searching behavior. Visser (1988) highlighted that starved and satiated phytophagous insects did not behave similarly in terms of seeking host plants. In *D. gallinae* the behavioral response to a substance detected by olfaction might vary according to the time since the last blood meal. To date, the effect of this factor has been tested on the toxic effects of essential oils on *D. gallinae* (more toxic as the time since the last blood meal increases, George *et al.* 2008), but not with regard to repellency. Testing the variation in behavioral response to repellent substances as a function of the physiological status of *D. gallinae* can allow a better understanding of the chemical interactions between *D. gallinae* and its environment.

5.2 Concentrations and ratios of compounds

The effect induced by a compound depends on its concentration and the duration of exposure to the mite (Deletre *et al.* 2016). Nechita *et al.* (2015) showed that the repellent effect of thyme essential oil decreases concomitantly with increasing dilution. Lee *et al.* (2019) studied the repellent effects of cinnamon bark oil, clove bud oil and their volatile organic compounds depending on the evaporation time. They showed that both of the essential oils are repellent regardless of evaporation time. However, two components of clove bud oil, eugenol and eugenol acetate, were found to change from having a repellent to an attractant effect over time in the experiment. The authors proposed that this may be partly explained by a difference in the dynamics of evaporation between the single compounds and the whole essential oil. Furthermore, Barimani *et al.* (2016) conducted a study to determine whether, and at what concentration, carvacrol, a compound known to be toxic to several arthropod pests (Ahn *et al.* 1998), can generate a toxic effect without being overly repellent. The aim was to implement a control strategy involving a trap containing carvacrol at toxic, but non-repellent levels. Whilst

traps containing 1% and 2% of carvacrol had a similar toxicity to mites, the former trapped more mites than the latter over two weeks.

Combinations of compounds and their ratios have an impact on compounds repellency against various arthropods (Deletre *et al.* 2016). Carvacrol-thymol combinations that differed with their ratio were tested against *D. gallinae* by Masoumi *et al.* (2016). Both thymol and carvacrol were significantly repellent alone and the combination of these two molecules had a synergistic effect for acaricidal purposes. However, no such synergy was observed when considering repellency (Masoumi *et al.* 2016). In short, the available studies on the effect of concentration and ratios of repellent substances against *D. gallinae* are limited and have only focused on four compounds (eugenol, eugenol acetate, carvacrol and thymol) and two essential oils (clove bud oil and thyme essential oil).

5.3 Ambient factors

Several studies have reported an impact of the humidity level on the olfactory capacities of certain insects, particularly *Anopheles gambiae* (Takken, Knols and Otten 1997) and *Ostrinia nubilalis* (Royer and McNeil 1993). Thus far, a single study has been carried out on the repellency caused by substances not derived from plants in *D. gallinae*, the entomopathogenic fungus *Beauveria bassiana* (Kilpinen and Steenberg 2016). Kilpinen and Steenberg (2016) tested the repellent activity (undifferentiated category) against *D. gallinae* produced by this biological agent using an experimental device that allowed the mite to come into contact with the conidia at two different relative humidity levels, alone or in combination with a desiccant inert dust. Addition of desiccant dust to the conidia significantly increased the repellency exerted by *B. bassiana*. Furthermore, the repellent effect of the fungi-dust combination was significantly higher at 85% than at 75% relative humidity (Kilpinen and Steenberg 2016).

Many other factors can influence the repellency of substances used against *D. gallinae* in poultry houses: e.g., the often fine and abundant dust present can buffer volatile compounds and compounds emitted from manure (e.g., NH_3), and/or the nature of the materials composing the building structure can interfere with some repellents (volatile molecules can be more or less fixed on surfaces depending on the material). We have not found any studies that specifically test these interactions. In addition, decomposition activity by microorganisms can interfere in a relatively unpredictable way, e.g., feathers that have remained in the litter for some time are more attractant to *D. gallinae* than fresh feathers (Koenraadt and Dicke 2010). It is important to keep in mind that, partly because of these diverse factors with unknown effects, results from laboratory experiments may not always transfer well to the field.

6 Framework on the integration of the repellent properties of substances of plant origin in Integrated Pest Management strategies for *D. gallinae*

Generally, the effect of repellent substances on a population of *D. gallinae* may be the result of different factors, depending on the type of repellency, the time in the life cycle of the pest and the mode of application of repellents in henhouses. True repellents can be used to develop methods that are based on remote interference. According to a mathematical model, an increase in the time between blood meals in female mosquitoes can have a significant effect on the population dynamics of this blood-feeding insect (Wan *et al.* 2014). If this also applies to *D. gallinae*, it is therefore possible to hypothesize that making the hen repellent or less attractive via plant-based feed supplementation (e.g., El Adouzi *et al.* 2019) could contribute to delay the population growth of *D. gallinae* by extending the duration of fasting between two blood meals and thus lengthening the time between laying or molting. Another hypothesis would be that pushing *D. gallinae* away from its microhabitats by means of true repellent substances could reduce the maximum size of infestation in farm buildings by limiting the availability of favourable habitats

and exposing mites to increased contact with conventional acaricides with biopesticides. To succeed in this direction, a method should be found to apply the repellent in the microhabitats in question, through local spray applications at the perch level or elsewhere, for example. Plant-derived true repellents could even be used in combination with attractants to develop “push-pull” approaches (Cook *et al.* 2007). The principle of push-pull involves combining an attractant and a repellent in a synergistic way, attracting pests to a “pull” stimulus whilst simultaneously repelling them with a “push”. In this way, individually moderate attractant and repellent properties can have a synergistic effect. Traps baited with a hen-mimicking attractant, for example, could attract more mites if deployed in combination with a repellent delivered to live hens (e.g., through feed supplementation) or the surrounding environment. A summary of repellent and attractant volatile compounds active on *D. gallinae* has recently been provided by Gay *et al.* (2020) and may help in identifying stimulo-deterrent product combinations for further development of push-pull approaches.

Irritants can be used to form local barriers, for example, to limit the access of mites to perches (to feed) or microhabitats (to rest), though they would need to be applied precisely and in a form that could provide a persistent effect, despite accumulation of dust and debris. They could possibly be used to make the skin of the hen less welcoming to *D. gallinae*, in the same way that certain products are used against mosquitoes (e.g., DEET, see DeGennaro 2015). Here again, the mode of application needs to be considered: finding a way to make an irritant emit directly from the hen through a *per os* administration would open up promising possibilities. Otherwise, direct application to the birds (e.g., by dipping them in a solution) may help to discourage the mite from biting the hen, but it is likely to be impractical at farm level where flock sizes number in the thousands.

Methodologically speaking, to state whether plant-derived repellents may be useful in controlling a pest, it is necessary (1) to conduct *in-vitro* experiments to state their repellent properties and, if possible, how mite-related and mite-independent factors interfere with them, (2) based on the obtained results, decide how and where to apply the substance on the farm, and (3) to verify that the properties measured *in vitro* have repercussions up to the level of the pest population under field conditions (here, in egg-laying henhouses). A relatively large body of literature from *in vitro* tests is already available: it is therefore possible, at least for the plants listed in Table 1, to derive data on their repellent properties against *D. gallinae*. However, for many of these products, further testing would be useful, especially as the type of repellency they exert has not been established. In addition, more work is needed on the different factors that may interfere with volatile compounds and affect the repellent properties of the test substances (e.g., physiological status of the mites, aggregation pheromone, ambient features). To date, very little information on these aspects is available for *D. gallinae*.

When considering field use of repellents it is important to consider both the strengths and limitations of *in vivo* experiments. A wide variety of factors, including the above ambient factors and others (e.g., seasonal variation and mite disease), can vary in the field regardless of the factor tested (e.g., repellency of a natural substance) and interfere with the experiment (unlike *in vitro* experiments, which are conducted under controlled conditions). The size of the pest population at the beginning of the experiment is generally unknown and heterogeneous between and within buildings or compartments (unless working on mite-free buildings and deliberately contaminating them with counted mites). Therefore, it is generally impossible to have a true control henhouse or control compartment. The high number of uncontrolled factors makes it difficult to carry out true replicates to distinguish the natural variation induced by the controlled factors from other factors. The population size of *D. gallinae* in the building is usually estimated by various sampling methods (generally by passive trapping; see Mul *et al.* 2015 for review) and compared before and after treatment. However, the pre/post treatment comparison does not eliminate uncontrolled concomitant factors that may have an impact on the estimated effectiveness of the treatment. It is therefore difficult to estimate the extent to which the observed results were actually induced by the treatment tested. Finally, the criterion chosen for evaluating the effect on *D. gallinae* is generally the change in the number

of individuals trapped over time. This aims to evaluate the evolution of the mite population size on the basis of sampling (taking into account the performance and limitations of the sampling method used). However, regardless of the sampling method used, since *D. gallinae* is an animal with a typically highly aggregated spatial distribution, it is very difficult to obtain a good representation of the level of infestation of the building through the trapped population (large disparities in the values obtained per trapping point are expected; thus, a very large number of traps is needed to obtain a good picture). Criteria related to production can be taken into account (e.g., laying rate and feed conversion), but their evolution over time is often too slow to capture the effects of moderate-impact treatments. Physiological indicators from the hens may also be taken into account, as it has been shown that the blood parameters, such as hematocrit or plasma corticosterone levels, are affected by mite infestations both in the wild (Potti *et al.* 1999) and on farms (Kowalski and Sokół 2009). On the whole, as trade-offs between rigor and feasibility must be made, it is then crucial to consider the results of field trials in the light of the experimental strengths and weaknesses to draw rational conclusions: levels of comparability between modalities with and without treatment (true controls available or not, confounding factors in case of before/after design) and natural variability estimated or not (presence or not of true replicates).

In short, by allowing the repellent properties and the mode of application of plant-originating repellents to control *D. gallinae* to be confronted, field studies are of undeniable importance. However, their realization requires careful consideration. Performing a sensible experimentation requires that the repellent properties (demonstrated in *in-vitro* tests), the targeted mode of action at the henhouse level, and the completeness and complexity of the farming system are taken into account.

7 Anticipating resistances to plant-derived repellents in *D. gallinae*

The sustainability of the efficacy of a treatment against pests (3rd principle of the IPM stated above; not to be confused with the persistence of products in the environment) depends largely on the speed of emergence of resistance. Resistance to pesticides is defined by the R4P network (researcher network for reflection and research on pesticide resistances) as “the heritable ability of an individual belonging to a pest species to survive a treatment applied correctly. When an individual is resistant to a [pesticide], it will be not (or little) affected by the treatment and will be able to produce viable offspring.” (R4P 2019). In field conditions, resistance results in the repeated failure of a product to achieve the expected level of control when it has been used according to its specific recommendations (IRAC 2020). Any product dedicated to controlling a pest exerts a selective pressure on its populations. This natural selection operates on the genotypic diversity initially available in the pest population and gradually leads to an increase in the frequency of genotypes that are tolerant to the control method, leading to the emergence of resistance within a pest population. In case of repellent activity, the selective pressure exerted by volatile compounds may lead to the increase in the frequency of genotypes that are insensitive (physiological inability to perceive the compounds) or that do not respond to perceived compounds (lack of repellent avoidance behavior).

Pesticide resistance in various pest arthropods is, and has been, the subject of numerous studies (REX Consortium 2007), but little is known about resistance to repellent substances. Only a few insects, including mosquitoes, bedbugs and cockroaches, have been studied for resistance to repellents (Stanczyk *et al.* 2010; Mengoni and Alzogaray 2018; Deletre *et al.* 2019; Vassena *et al.* 2019, Yang *et al.* 2019). These pioneering studies on insects, including two blood-feeding micropredators (mosquitoes and bedbugs), are likely to provide valuable insights to effectively advance the exploration of this topic in *D. gallinae*. Most of these studies have focused on synthetic repellents, although Deletre *et al.* (2019) also included plant secondary metabolites in their work.

N,N-Diethyl-m-toluamide (DEET) is the most commonly used active ingredient in insect repellents. Resistance to DEET has been reported in mosquitoes, bedbugs and cockroaches (Stanczyk *et al.* 2010; Mengoni and Alzogaray 2018; Deletre *et al.* 2019; Vassena *et al.* 2019, Yang *et al.* 2019). All of these studies demonstrated significant differences in behavioral responses to DEET amongst populations of the insects studied. In addition, Stanczyk *et al.* (2010) experimentally demonstrated that the “insensitive” trait to DEET was hereditary, dominant in *Aedes aegypti* and based on a change in the function of one sensilla.

Interestingly, cross-resistance was reported between neurotoxic insecticides (pyrethroids, organophosphates) and repellent substances in all three aforementioned insect taxa (mosquitoes, bedbugs and cockroaches; Mengoni and Alzogaray 2018; Deletre *et al.* 2019; Vassena *et al.* 2019, Yang *et al.* 2019). In these studies, insecticide-resistant populations of *Aedes aegypti* (mosquito), *Cimex lectularius* (bedbug) and *Blattella germanica* (cockroach) were shown to be less responsive to repellents than susceptible populations of the same taxa. Yang *et al.* (2019) have also reported a decreased antennal sensitivity in populations of *Ae. aegypti* that were resistant to both pyrethroids and DEET, as well as to three other synthetic repellents. Several compounds contained in plant essential oils, and known for their repellent properties against *D. gallinae* (e.g., geraniol, eugenol), have been shown to have true neurotoxic effects on insects, with molecular and cellular targets common to those of synthetic insecticides (López and Pascual-Villalobos 2010, Regnault-Roger *et al.* 2012). Cross-resistance between plant-derived repellents and synthetic insecticides, especially when target-site resistance is involved, can therefore be explained by the functional basis of the latter.

However, consistent with this hypothesis, the effect of target protein modification is not always a decrease in susceptibility to repellents. In another mosquito (*Anopheles gambiae*), for example, Deletre *et al.* (2019) found an increase in sensitivity to certain repellents in mutant genotypes displaying target-site pyrethroid and organophosphorus resistances due to the *kdr* mutation in the voltage-dependent sodium channel and the *Ace* mutation in acetylcholinesterase, respectively. In cases of target-site resistance, the target protein of the insecticide has a slightly modified amino acid sequence compared to the same protein in a susceptible individual, thereby inducing a decrease in the affinity of the pesticide. The alleles of the coding gene often differ between susceptible and resistant types by a simple nonsilent point mutation at a key site of the interaction between the two molecules. Thus, although plant-derived compounds can affect the same proteins as synthetic insecticides, they most likely do not do so in the same way (not at the same sites of action). Additionally, pleiotropic effects (single genes affecting multiple systems or determining more than one phenotype) of the alleles conferring insecticide resistance may also explain these patterns (Deletre *et al.* 2019). Whatever the reason, it is not surprising that variations in protein-coding genes of the nervous system can affect the susceptibility to insecticides and repellents in a variety of ways, sometimes in contradictory directions.

We can therefore conclude that, at least in mosquitoes, target resistance to neurotoxic insecticides may be associated with resistance to repellents, but also with increased susceptibility to repellents. As there are several mutations responsible for target resistance to pyrethroids in *D. gallinae*, and as they are relatively frequent in several regions of the world (Katsavou *et al.* 2020), taking these genotypes into account when assessing the risk of resistance developing to plant-derived repellents will constitute a point of interest for further work in this area.

8 Conclusions

Several repellent substances, including some true repellents, have been identified thus far via *in vitro* tests with *D. gallinae*, including *Commiphora holtziana* spp. *holtziana* gum, extracts of *Conocarpus erectus*, and several essential oils, including those from thyme, *Nepeta cataria* and *Artemisia sieberi*. Various factors (e.g., concentration, humidity, dust density, and interactions with pheromones emitted by congeners) are likely to interfere with this repellent effect, but very few studies have considered these thus far.

The properties of these repellent substances align well with the need to develop “non chemical” control strategies against this pest, promoting IPM in the egg laying sector as has been done in various farming industries, such as horticulture. However, to take advantage of these products in henhouses, it is important to define how we expect repellents to operate (i.e. to repel mites from their host, or from their preferred habitat) and to cross-reference this with the type of repulsive properties we seek to deliver: Are we looking to reduce the use by *D. gallinae* of small, well-defined areas (irritant properties), for example, or aiming to divert mites away from an odor source (true repellent properties)? In addition, other properties, which have not been studied thus far in studies on plant-derived substances against *D. gallinae*, could be incorporated into IPM strategies (odor masking, antifeedants). Once these properties have been verified on a small scale (lab tests) and the strategy defined, the effectiveness of the mode of action at full farm system scale must also be verified through field trials. This requires careful and considered experimental design and rigorous implementation to obtain unambiguous results, this being difficult to achieve on commercial farms.

Plant-based products have been used for several years as in-feed supplements to reduce the attractiveness of hens to *D. gallinae*. In contrast, to the best of our knowledge, no repellent is specifically recommended for premise application in this mite’s habitat, and no push-pull strategy has been developed thus far. In general, the available knowledge on the repellent properties of plant-derived substances on *D. gallinae* is relatively sparse and relies almost exclusively on *in vitro* tests, often without distinction between types of repellency. The lack of larger-scale experiments presents a clear knowledge gap and makes it very difficult to comment on the future commercial potential of repellents for *D. gallinae* control.

Finally, the risk of resistance emergence to natural repellent substances would be worth assessing to implement sensible IPM strategies against *D. gallinae*. Resistance to synthetic neurotoxic substances (conventionnal acaricides) has already been reported in several insect taxa, as well as in mites, including *D. gallinae*. Resistance to repellents (synthetic and plant-derived) has also been found in insects, but has not been studied in mites to date. Importantly, cross-resistance between repellents in general and commonly-used neurotoxic insecticides has been reported repeatedly, and may be explained by physiological functions in the nervous system. Given that resistance to common neurotoxic molecules used against mosquitoes is known to also occur in *D. gallinae*, further work in this area could be recommended.

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