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Plant Secondary Metabolites as Rodent Repellents: a Systematic Review

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Abstract The vast number of plant secondary metabolites (PSMs) produced by higher plants has generated many efforts to exploit their potential for pest control. We performed a systematic literature search to retrieve relevant publications, and we evaluated these according to PSM groups to derive information about the potential for developing plant-derived rodent repellents. We screened a total of 54 publications where different compounds or plants were tested regarding rodent behavior/metabolism. In the search for widely applicable products, we recommend multi-species systematic screening of PSMs, especially from the essential oil and terpenoid group, as laboratory experiments have uniformly shown the strongest effects across species. Other groups of compounds might be more suitable for the management of species-specific or sex-specific issues, as the effects of some compounds on particular rodent target species or sex might not be present in non-target species or in both sexes. Although plant metabolites have potential as a tool for ecologically-based rodent management, this review demonstrates inconsistent success across laboratory, enclosure, and field studies, which ultimately has lead to a small number of currently registered PSM-based rodent repellents.

Keywords Essential oils · Herbivory · Plant secondary metabolites · Rodentia · Repellents · Review · Vertebrate pest management

Introduction

Satisfying the dietary needs of the world's growing population in the twenty-first century requires an increase in agricultural production. In 2014, about 2.5 billion tons of grains were harvested worldwide, with only 43 % of the crop used as food because grain also is processed for animal feed, fuel, and industrial raw materials. Today, about one third of the Earth's land mass is used for agriculture (http://data.worldbank.org/). Data from the Food and Agriculture Organization of the United Nations demonstrate that 3 % of the globe's land surface (13 billion ha) is used for permanent crops (Roser 2016). To elevate food production in accord with population growth, the utilization of existing agricultural land needs to be optimized, for example, by minimizing the effect of disease and crop pests.

Significant agricultural pests include arthropods and vertebrates, especially rodents. The number of rodent species causing problems that require management is small. Only about 5 % of rodent species worldwide pose a significant risk to humans (Singleton et al. 2007). These species include commensal rodents that are present close to man-made infrastructure, such as Norway rats (*Rattus norvegicus*), black rats (*R. rattus*), and house mice (*Mus musculus*), as well as field rodents including ricefield rats (*R. argentiventer*), multimammate mice (*Mastomys* spp.), and the lesser bandicoot rat (*Bandicota bangalensis*) that can cause chronic damage (Buckle and Smith 2015). In some cases, damage only occurs when massively overabundant populations build up during population outbreaks in temperate regions (Delattre

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et al. 1992; Singleton and Brown 2005; Singleton et al. 2007) and in the tropics (Doungboupha et al. 2003; Leirs et al. 1997).

Adverse effects of rodents are manifold and include pre-harvest crop damage, and post-harvest damage to stored products and infrastructure. Pre-harvest rodent damage is particularly prevalent in Asia and Africa (Singleton et al. 1999). Pre-harvest losses in Asia result in a reduction in rice yield of 5–20 % (Singleton et al. 2003). This equals an annual loss of 77 million tons (John 2014) – enough food to feed 200 million people for a year (Singleton et al. 2003). Population densities of both house mice in Australia and common voles (*Microtus arvalis*) in Europe can exceed 2000 animals per hectare (Bryja et al. 2005; Saunders 1983). In such a scenario, pre-harvest damage in Europe probably tops several hundreds of millions of Euros (€) (Jacob et al. 2014) and 60 million US$ in Australia (Brown et al. 2000). Outbreaks of bamboo rats in Asia have more dramatic effects because food competition of rodents with livestock and people that can result in widespread famine (Singleton et al. 2010). Post-harvest losses occur when commensal rodents consume stored goods or through the contamination of produce. Rodent damage to infrastructure by musk rats (*Ondatra zibethicus*) is estimated at about 599 million € and 3.35 billion € by *Rattus* spp. per year in the EU (Kettunen et al. 2009).

In addition, rodents contribute to health problems for humans, livestock, and companion animals through the transmission of zoonotic disease (Meerburg et al. 2009). Pathogens include viruses: e.g., hantavirus, tick-borne encephalitis virus, hepatitis E virus; bacteria (e.g., *Leptospira*, *Borrelia*, *Rickettsia*) and parasites (e.g., toxoplasmosis, giardia infection, echinococcus infection) (Meerburg et al. 2009). The cost associated with the transmission of rodent-borne diseases is assumed to be similar to the losses due to rodents in plant production (Bordes et al. 2015). The annual cost of rodent related pre-harvest and post-harvest damage, losses of stored goods, and expenditure for disease prevention and treatment is likely to exceed 23 billion US$ (Jacob and Buckle 2016).

Due to the adverse effects of rodents on plant production and public health, rodent management is critical in many cropping systems and in urban situations around the world (Buckle and Smith 2015). Although large-scale measures of rodent management in an agricultural context include agricultural practices that render habitat temporally unsuitable for rodents (e.g., ploughing) and bio-control (e.g., promoting predation), they rely mainly on the application of rodenticides to reduce damage to crops. For the management of commensal rodents in urban and rural areas, anticoagulant rodenticides often are the weapon of choice, although the increased occurrence of resistant populations poses an enormous challenge to future strategies. A major problem caused by the use of poison is the risk to non-target species either by direct ingestion of poisonous bait or indirectly through the consumption of poisoned prey or carrion. There are reports of secondary poisoning caused by anticoagulants worldwide (e.g., Eason et al. 2002; Geduhn et al. 2015) that are of conservation and biodiversity concern.

The problems associated with the use of poison to manage populations and efforts to increase efficacy of rodent control have culminated in a call for ecologically-based rodent management (Singleton et al. 1999) that uses a toolbox of techniques that are ecologically, socially, and economically appropriate.

Potential of Plant Secondary Metabolite as Rodent Control Tools

One of the promising rodent control tools is the application of plant secondary metabolite (PSM) odor mixtures that deter rodents from feeding on crops or destroying infrastructure. Despite numerous candidate compounds that affect individual fitness (Ostfeld and Canham 1995), reproduction (Diawara and Kulkosky 2003), or behavior (Takahashi and Shimada 2008), the development of products for field application is hampered by a complex mosaic of confounding factors, recently laid out by DeGabriel et al. (2014). These factors include profound differences in adaptations of different herbivore species to different PSMs. These differences reach even higher complexity because of differences in sex, age, and reproductive status of the animals, and may vary seasonally with the spatial and temporal availability of food and changes in food chemical composition (DeGabriel et al. 2014).

On small scales, repellents based on PSMs that are less toxic than rodenticides may provide a viable, cost-effective, and ethically acceptable alternative to the use of poison or labor intensive trapping. For example, Epple et al. (1996) successfully repelled pocket gophers (*Geomys bursarius*) from gnawing on cables by using pine needle oil, which also has potential as a commercial repellent for snowshoe hares and voles (Bell et al. 1987). Willoughby et al. (2010) used capsaicin to deter wood mice (*Apodemus sylvaticus*) from consuming valuable tree seeds.

Some compounds are regarded as highly toxic (e.g., cardenolides common in Plantaginaceae, alkaloids in Solanaceae, cyanogenic glucosides in Fabaceae), while others have negative impacts on fecundity (e.g., plant steroids in Ranuculaceae) or on various compounds that affect enzymes (e.g., polypeptides and non-protein amino acids in Fabaceae). If such compounds are ingested, there may be negative effects on predators or on the environment similar to anticoagulant rodenticides. To prevent such negative unintentional effects, less harmful compounds that function before or shortly after ingestion by their odor (e.g., terpenoids or glucosinolates) or taste (e.g., tannins, low molecular phenolics) seem to be more promising substances. Some compounds, especially those with a characteristic repellent odor (essential oils and terpenoids), may be useful for prevention against rodent damage, because these odors disseminate through the environment without further action required. Such sensory repellents are highly volatile and affect the mucous membranes of the eyes, nose, mouth, and throat of animals before feeding (Mason et al. 1996). Taste-based plant-derived repellents generally include a bitter or hot-tasting ingredient that affects the same membranes, but they act after ingesting.

There also are described predator odors that are repellent to rodents (Nolte et al. 1993, 1994a, b), especially when they match the odors of the target species' natural predators (Apfelbach et al. 2005). Mostly, compounds from urine, feces, and anal gland secretions are used, but these products are difficult to obtain, and often commercial products are based on chemicals that contain sulfur (Wagner and Nolte 2001), which seem to trigger avoidance behavior in rodents. There have been some applications of such products for the protection of crops and other resources. Essential oils and terpenes may function similar to "predator odors" as post-ingestive repellents because they cause rodents to become place aversive or food aversive. Phenols can be used only as food aversive, as the animal has to ingest them first and then be repelled by the taste.

Modes of Action and Adaptation Several modes of action determine the effectiveness of PSMs in repelling herbivores. Pre-ingestive effects cause deterrent impact on animals before the food item is ingested. These are due mainly to the odor of volatile compounds (e.g., terpenoides). Deterrent effects caused by taste (e.g., bitterness of low molecular phenolics, alkaloids, or astringency of tannins) usually are regarded as post-ingestive effects. Some of the latter have negative impact on the digestion of nutrients or on the bacterial community of the gastro-intestinal tract (e.g., tannins, terpenoides, pre-absorptive effects), while others have negative impact due to their toxicity (e.g., cardenolides post-absorptive effects) with far reaching physiological consequences (Palo and Robbins 1991).

Herbivores have evolved adaptations in feeding behavior that avoid malaise or toxication caused by PSMs. Individual responses to PSMs are governed by several mechanisms (reviewed by Dearing et al. 2005) and include conditioned aversion that dictates how the individual will react to the compound at the next encounter (Baker et al. 2007). Animals can learn to associate taste with discomfort, which leads to reduced food intake. This process is known as conditioned food aversion (Garcia et al. 1955). It has been demonstrated in different herbivorous mammals, e.g., house mice (Watkins et al. 1998), goats (Provenza et al. 1990), and sheep (Kyriazakis et al. 1998). Simply avoiding or reducing consumption of plants or parts of plants with particular compounds is the most obvious herbivore behavior (Marsh et al. 2006; Wiggins et al. 2003). Another is choosing plants with low toxin concentrations (Moore and Foley 2005; Stolter et al. 2005, 2013). Still another is decreasing the feeding rate when exposed to the odor of a non-preferred food plant, (pre-ingestive effect, Edlich and Stolter 2012; Hansen et al. 2015, 2016) or to increased concentrations of PSMs (Stapley et al. 2000; Wiggins et al. 2003). Negative physiological consequences of compounds also affect the food intake of an animal via a feedback loop. Enhanced plasma concentration of the toxin (McLean et al. 2007), activation of the emetic system (Provenza et al. 1994), or possibly acidosis (Foley 1992) can lead to negative consequences. Consequently, animals can learn through physiological feedback to manage intake of plants with toxic metabolites.

Metabolism and excretion, the physiological processes used to eliminate ingested compounds from the body, are better adapted in animals with a high PSM intake (e.g., specialists and browsers) than in generalists and grazers, which encounter only a limited amount of PSMs (Iason and Villalba 2006). For example, enzymes metabolize toxins into products for rapid excretion (McLean and Duncan 2006). Thus, herbivore specialists, such as koalas [*Phascolarctos cinereus* (Marsh et al. 2007)] or woodrats [*Neotoma* spec. (Sorensen et al. 2005)] can cope with higher toxin concentrations than generalists either through different feeding behavior or by anatomical and physiological means (Marsh et al. 2003). The ability of herbivores to reduce the absorption of toxins via the gut is well known to pharmacologists (Wagner and Nolte 2001) but such studies are under-represented in the plant-animal scientific literature.

In this review, we systematically scanned the literature for PSM-based principles of plant defenses against rodents. We evaluated this information to highlight common features of compounds that are efficient in repelling rodents, and we discuss where to focus future work to develop effective repellents based on PSMs.

Methodology

Literature Search We performed a systematic literature search to retrieve relevant publications from the ISI Web of Science (WoS) scientific publication database via the Thomson Reuters Web of Knowledge platform (http://www.webofknowledge.com). Within the platform, we included six databases (Web of Science ™ Core Collection, Biological Abstracts ®, CABI: Cab Abstracts®, FSTA®- the food science resource, KCI- Korean Journal Database, and SciELO Citation Index). We considered publications associated with "rodents and repellents and with plant secondary metabolites", from documents published January 1910 to January 2016. No language restrictions were applied. The following topics were used to search titles abstracts and keywords: Topic 1: rodent* or mice or mouse or rat* or vole or squirrel or beaver or gopher or hamster or dormice or "guinea pig"; and Topic 2: repel* or repellent or avoid* or deterrent or antifeedant or defense; and Topic 3: plant secondary metabolite or plant secondary compound or secondary plant metabolite. The search was run on 14th January 2016. The initial database search yielded 977 publications.

Selection of References For identifying the relevant studies, one author (SH) reviewed all titles and abstracts that resulted from the search. From these, 917 publications were rejected on initial screening because title and/or abstract indicated that the publication did not meet the topics. The evaluation of the full text articles was conducted by SH, CS, and CI to further refine results based on the PSM group considered in the publication. After evaluation of the full text, six further publications were excluded because they were not related directly to rodent feeding behavior. In total, 54 relevant studies were included in the systematic review that belonged to eleven PSM groups (Fig. 1). The publications were organized according to PSM group (Fig. 1), compound, or plant of concern, animal species, reference and year of publication, type of study (laboratory, enclosure, field), and major result regarding repellent properties (Supplementary Table S1).

Summary of Chemical Results

The literature search showed that there has been increased scientific interest in PSM application in rodent management during the last 15 years. This may be a result of increasing conservation and ethical concerns regarding the use of lethal methods and associated economic, public, and political pressure to develop suitable alternatives. The main focus of all studies has been the effect of potential plant-derived repellents on rodent feeding behavior.

Effectiveness of PSMs

Plants and Plant Materials

Some studies have aimed to quantify the effect of PSMs on feeding and some to examine the exact mechanisms for these plant-animal interactions by using different methodological approaches. In 19 of 22 studies, fresh parts of plants were offered directly to animals; in four, food intake was analyzed through manipulated diets. There were only two studies that identified specific plants that act as feeding deterrent (Curtis et al. 2002; Dearing et al. 2001) and 12 where plant material had an effect on rodents (Table 1; Supplementary Table S1). Apart from studies that used whole plants or plant material, several groups of compounds have been considered in rodent research. They include essential oils and terpenoides, alkaloids, alkylamides, (di)carboxylic acids, glucosinolates, and phenolics.

Essential Oils and Terpenoides

This diverse group includes compounds from a range of plant species that were studied almost exclusively in laboratory experiments (Table 2; Supplementary Table S1). Epple et al. (1996), for example, used pine needle oil, containing α- and β-pinene, to repel pocket gophers from gnawing on cable insulation. Kelsey et al. (2009) demonstrated the avoidance of PSMs by rodents by the removal of needle resin ducts before consumption. Fischer et al. (2009, 2010, 2011a, b, 2013a) reported that a multitude of terpenes (as well as ketones) prominent in essential oils have a repelling effect in a laboratory two choice test (e.g., geranium oil, black pepper oil), although combinations of both substances did not increase the repelling effect. Similar results were achieved by Hansen et al. (2015) who identified four plant odors of essential oils (black pepper, bergamot, fennel, neem) that repelled common voles. Three of the tested essential oils also repelled house mice (bergamot, bucco, fennel) under laboratory conditions (Table 2). In a field trial, Fischer et al. (2013b) demonstrated that terpenoides can be used in an outdoor application to repel the fossorial common vole from experimental plots. The observed effect lasted for about four to five days.

Alkaloids, Alkylamids

Guimarães et al. (2003) found a repelling effect of the total quinolizidine alkaloids (QA) of *Ormosia arbora* seeds in a field experiment. Feeding trials by Janzen et al. (1990) revealed only a mild effect of polyhydroxypyrrolidine alkaloid (DMDP) found in seeds of *Lonchocarpus* species in the Brazilian rainforest (Table 3; Supplementary Table S1). Alkylamides from extracts of Szechuan pepper (*Zanthoxylum piperitum*) had a strong post-ingestive repelling effect on Norway rats (Epple et al. 2001) (Table 3; Supplementary Table S1).

(Di) Carboxylic Acids

Fanson et al. (2008) demonstrated that several environmental factors influence the foraging behavior of two African rodents. Oxalic acid treated popcorn kernels were avoided by woodland thicket rats (*Grammomys dolichurus*) and Cairo spiny mice (*Acomys cahirinus*) (Supplementary Table S1).

Glucosinolates

This group has been intensively studied in laboratory trials by Samuni-Blank et al. (2012, 2013a, b, 2014). They elucidated different aspects of the multi-layered effects of glucosinolates

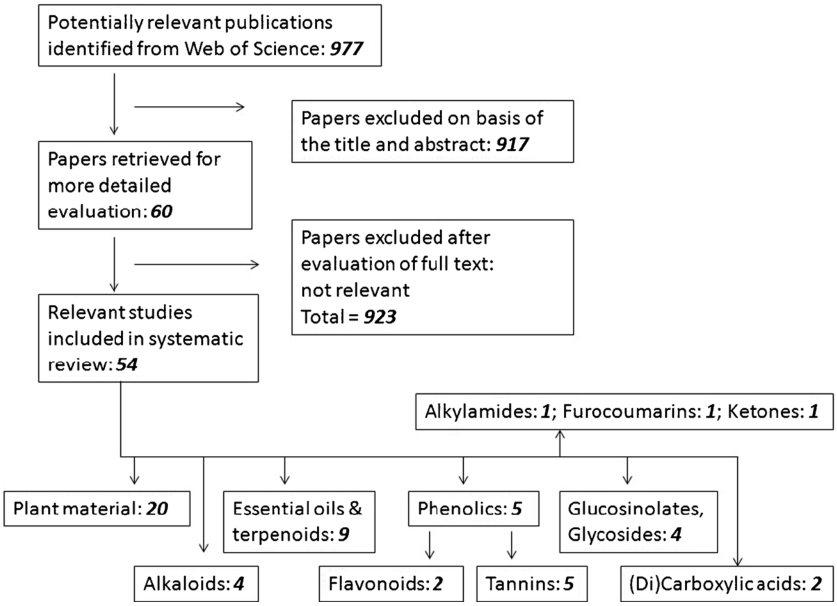

Fig. 1 Flow chart of publication selection process (adapted from Van Cauwenberghe et al. 2010)

(GLS) in the seeds of the *Ochradenus baccatu* tree. Glucosinolates are found in many plant families, and usually are thought to have little repellency. However, as part of a compartmentalized defense system that is activated by damage to plant tissue and subsequent hydrolysis of GLS, several toxic compounds are released that affect herbivores. This "mustard bomb" has been demonstrated to be effective in its interspecific repelling effect, although there are species-specific evolutionary adaptations to this defense mechanism (Samuni-Blank et al. 2013a). While seed predators show an increased physiological tolerance towards the released toxins, others have developed behavioral responses and avoid damaging intact seeds (Samuni-Blank et al. 2013a). In this series of publications, the authors have highlighted the ecological divergence in responses to plant defense mechanisms (Supplementary Table S1).

Phenolics – Low Molecular Phenolics and Flavonoids

Seven specific compounds, two phenolic groups (stilbenes, phenolic resins), and total phenolics have been tested against nine rodent species (Table 4; Supplementary Table S1). For three compounds, a negative impact on feeding behavior was reported (cinnamamide, anthraquinone, and one unknown). The results show deterrent effects on female common voles but not on male voles or house mice (Hansen et al. 2015, 2016). These results underpin the necessity of validating effects for all target species and sexes. Cinnamamide showed a strong repellent effect against wild Norway rats (Crocker et al. 1993) and is known as 'non-lethal mouse repellent' (Gurney et al. 1996) because of its low toxicity. Other studies have confirmed the repellent effect of cinnamic aldehyde against house rats (Babbar et al. 2015). It could not be determined whether the specific mechanism of the cinnamic aldehyde effect is via taste or odor. Despite this fact, these compounds should be useful in rodent management for protecting crops, stored products, and farm structures where other pesticides would be too hazardous. All the other tested compounds (e.g., salicortin, salicin) showed no repellent effects. Additionally, stilbenes and creosote resin are reported to have negative effects on field voles (*Microtus agrestis*) and woodrats (*Neotoma lepida, N. stephensi, N. albigula*), and the concentration of total phenolics seems to be important for the avoidance of these plants by *Microtus oeconomus* (Dai et al. 2014) (Table 4). Bergeron and Jodoin (1991) tested quercetin with *Microtus pennsylvanicus,* and Basey et al. (1988, 1990) tested tremulacin and tremuloidin with *Castor canadensis.* These studies showed no repellent effect of these specific flavonoids. The secondary metabolites of *Lonchocarpus*, however, contain seven types of flavonoids, which were found to be responsible for the strong avoidance of *Lonchocarpus* seeds by spiny pocket mice (Janzen et al. 1990).

Phenolics – Tannins

Of the nine studies dealing with tannins, seven were conducted with the hydrolyzable tannin, tannic acid, using eight rodent species (Table 5; Supplementary Table S1). Four were conducted as laboratory experiments; the others were field studies, and all of them used artificial food. Due to the fact that tannic acid has a negative post-ingestive effect it has been assumed that rodents should decrease their food intake when exposed. However, only one of the experiments (Bozinovic 1997 with *Octodon degus* and *Phyllotis darwini*) demonstrated explicit repellent results. Two studies used plant materials

Table 1 Effect of plant material reported in 20 of 54 studies based on laboratory experiments (L), enclosure experiments (E) or field experiments (F)

Compound(s) / Plant(s)	Animal species	Author	Year	L/ E/ F	Result
Betula pendula	*Microtus agrestis*	Rousi et al.	1993	L	Fertilization increase & shading decreased palatability of seedling bases
Betula pendula	*Microtus agrestis*	Tiainen et al.	2006	E	No effect
several *Betula* species	*Microtus agrestis*	Laitinen et al.	2004	E	Birch species differed in general susceptibility to browsing
Capsicum spp.	Mammals	Levey et al.	2006	F	Deterred by naturally occurring fruits
Carex aquatilis, *Salix pulchra*, *Ledum palustre*	*Lemmus sibiricus*, *Dicrostonyx torquatus*, *Microtus oeconomus*	Jung and Batzli	1981	L	No effect; *L. palustre* toxic
Several plants	*Microtus ochrogaster*	Curtis et al.	2002	L	Repellent effect*
Helianthus annuus, *Arachis hypogaea Juglans regia*	*Rattus norvegicus*	Grant-Hoffman and Barboza	2010	L	Repellent effect to walnuts
Helleborus foetidus	*Apodemus sylvaticus*	Fedriani and Boulay	2006	L	Repellent effect of unripe fruits
Quercus rotundifolia, Quercus faginea, Quercus suber	*Apodemus sylvaticus*	Rosalino et al.	2013	E	Repellent effect of acorn with tannins
Juniperus monosperma	*Neotoma stephensi, N. albigula*	Dearing et al.	2001	L	Repellent effect*
Juniperus monosperma	*Neotoma stephensi, N. albigula*	Boyle and Dearing	2003	L	No effect
Several plants	*Neotoma fuscipes*	Brooke McEachern et al.	2006	L	Repellent effect of novel-chemically-defended plants
Several plants	*Microtus ochrogaster*, *M. pennsylvyticus*	Lindroth and Batzli	1986	E/L	No intake effect, reduced growth rate
Picea abies, *Abies alba*	*Sciurus vulgaris*	Rubino et al.	2012	F	Limonene in fir seeds seemed to act repellent
Several plants	*Microtus agrestis*, *Clethrionomys glareolus*	Vehvilainen and Koricheva	2006	F	Target tree species mixed with a less palatable species, damage is reduced
Several plants	*Microtus arvalis orcadensis*	Hartley et al.	1995	L	Voles can detect variation in chemical composition
Pinus sylvestris	*Clethrionomys glareolus*	Iason et al.	2011	E	No effect
Several *Salix* species	*Myodes glareolus*	Shaw et al.	2013	F	No effect
Several plants	*Geomys attwateri*	Rezutek and Cameron	2011	F	No effect
Several plants	*Microtus agrestis, Clethrionomys glareolus*	Hjältén and Palo	1992	F	Repellent effect of high nitrogen concentrations

*to a experimental control

Table 2 Effect of essential oils and terpenoids reported in 10 of 54 studies based on laboratory experiments (L) or field experiments (F)

Compound(s) / Plant(s)	Animal species	Author	Year	L/ E/ F	Result
α-pinene, β-pinene, myrcine	*Geomys bursarius*	Epple et al.	1996	L	Repellent effect*
α-pinene	*Neotoma stephensi, N. albigula*	Sorensen and Dearing	2003	L	No effect
Black pepper oil (BPO), bergamot oil, buchu oil, fennel oil, grass-tree oil, (*R*)-(+)-Limonene, neem oil	*Microtus arvalis*, *Mus musculus*	Hansen et al.	2015	L	Repellent effect in voles*: BPO, bergamot oil, fennel oil, neem oil; repellent effect in mice*: bergamot oil, bucco oil, fennel oil
Black pepper oil, Chinese geranium oil, onion oil	*Arvicola amphibius*	Fischer et al.	2009, 2010, 2011a, b; 2013a, b	L	Repellent effect*
Monoterpene, sesquiterpene, diterpene from *Pseudotsuga menziesii*, *Tsuga heterophylla* and *Picea sitchensis*	*Arborimus longicaudus*	Kelsey et al.	2009	F	Resin avoided by removing ducts

*to a experimental control

containing tannins that were tested against *Apodemus speciosus* and *Microtus oeconomus*. They either produced ambiguous results or showed no effects. Tannins, especially "condensed tannins", are complex molecules, and nearly every deciduous plant species has a specific pattern. This complexity hampers testing tannins as possible feeding deterrents because specific compounds are often unknown and not available on the market.

Differences in Experimental Design and Impact on Results

Of the 54 relevant references identified in our systematic literature search, there were 32 cage studies, 6 studies in outdoor enclosures, and 13 in the field. In three studies, rodents were not involved directly in any experiments (Kelsey et al. 2009; Levey et al. 2006; Rubino et al. 2012) but since they were based on feeding observation of animals that avoided certain plants they were considered in the review.

Laboratory Studies Laboratory cage studies allow the screening of compounds/concentrations with relatively small numbers of animals, and they can yield rapid results. A comparison of laboratory studies shows considerable differences in methodology in regard to sample size. Sometimes sample size was unspecified (Diawara and Kulkosky 2003; Schmidt et al. 1998; Tiainen et al. 2006), or minimal ($N = 3$ of one sex, Dai et al. 2014). Sometimes only females were considered because of their importance in population dynamics (Diawara and Kulkosky 2003; Hansen et al. 2015). Most studies, however, included both sexes, although sex-specific effects were not always reported (Bergeron and Jodoin 1991; Boyle and Dearing 2003; Curtis et al. 2002; Dai et al. 2014a; Epple et al. 1996; Fedriani and Boulay 2006). However, such reporting is confounding because males and females may react differently to PSMs (Hansen et al. 2016; Shumake and Hakim 2000;), and combining data for males and females masks sex-specific effects.

Secondary metabolites often are investigated by providing either fresh or thawed plants, or plant parts, or food manipulated with metabolites to experimental animals. Feeding experiments usually are carried out in no-choice, two-choice, or cafeteria feeding experiments. Generally, we prefer multiple choice tests, as animals almost always have a choice of several food sources in nature. In no-choice tests, where the only

Table 3 Effect of alkaloids, alkylamides reported from 5 of 54 studies based on laboratory experiments (L) or field experiments (F)

Compound(s) / Plant(s)	Animal species	Author	Year	L/ E/ F	Result
Caffeine, rauwolfia alkaloids	Laboratory ICR Swiss mouse	Freeland and Saladin	1989	L	No effect
Gramine	*Microtus pennsylvanicus*	Bergeron and Jodoin	1991	L	No effect
Polyhydroxypyrrolidine alkaloid (DMDP)	*Liomys salvini*	Janzen et al.	1990	L	Mild repellent effect*
Quinolizidine alkaloids (QA); sparteine, angustifoline, lupanine, ormosanine, panamine	*Dasyprocta leporina*	Guimarães et al.	2003	F	Repellent effect for seeds with QA
Zanthoxylum piperitum	*Rattus norvegicus*	Epple et al.	2001	L	Strong post-ingestive repellent effect*

*to a experimental control

Table 4 Effects of phenolics (low molecular phenolics and flavonoids) reported in 8 of 54 studies based laboratory experiments (L) or field experiments (F)

Plants/ Compounds	Animal species	Author	Year	L/E/ F	Result
Anthraquinone	*Microtus arvalis, Mus musculus*	Hansen et al.	2015	L	Repellent effect in female common voles*
Cinnamic acid, Cinnamamide, ferulic acid	*Rattus norvegicus*	Crocker et al.	1993	L	Repellent effect of cinnamide
Creosote resin (phenolic resin)	*Neotoma lepida*	Meyer and Karasov	1989	L	Repellent effect*
Creosote resin (phenolic resin)	*Neotoma stephensi, Neotoma albigula*	Torregrossa et al.	2012	L	Repellent effect*
Several plants	*Microtus oeconomus*	Dai et al.	2014	L	Repellent effect total phenolics
Salicin, salicortin	*Castor canadensis*	Basey et al.	1988	F	Site dependent effect
Salicin, salicortin Unknown phenolic	*Castor canadensis*	Basey et al.	1990	F	Repellent effect of unknown compound of plant regrowth
stilbenes	*Microtus agrestis*	Virjamo et al.	2013	(F)	Repellent effect for higher concentrations of stilbene

*to a experimental control

option is to eat or to starve, animals can overcome their initial reluctance and learn to accept foreign odors and mild adverse effects of PSMs (Gurney et al. 1996).

Enclosure Studies Enclosure experiments are conducted under conditions resembling the natural environment more closely than laboratory cage trials and may provide more robust results. However, they are time consuming and require appropriate infrastructure. Most outdoor enclosure experiments have focused on rodent damage to seedlings, assessing the effect of culture conditions (Iason et al. 2011; Laitinen et al. 2004), replanting (Virjamo et al. 2013), or seedling size (Tiainen et al. 2006).

Field Studies Field experiments should yield the ultimate information whether a particular compound or a combination of compounds effectively repels rodents, but they require substantial effort and are subjected to more variability than cage and enclosure trials. Field methods range from observational studies (Basey et al. 1988; Guimarães et al. 2003; Levey et al. 2006; Rubino et al. 2012), manipulated field plots (Hjältén and Palo 1992; Rezsutek and Cameron 2011; Shaw et al. 2013), and feeding experiments (Barthelmess 2001; Basey et al. 1990; Fanson et al. 2008; Samuni-Blank et al. 2012; Schmidt et al. 1998) to the application of product prototypes, e.g., methyl nonyl ketone (Fischer et al. 2013b).

Methodology Recommendations Differences in methodology are due primarily to differences among target species, management systems, and based on the general aim of the study that is related to rodent management. However, some general strategies for screening potential PSM are possible. First, wild caught (DeGabriel et al. 2014) or possibly the F_1 generation males and females of the target rodent pest species should be tested in laboratory cage trials. Second, promising plant-derived repellents need to be tested under semi-natural conditions, and if successful, in the field with the specific target species. We recommend this sequential approach of cage – enclosure – field trials, and only continuing the study with a particular metabolite when results are positive. Lindroth and Batzli (1986), however, used the reverse approach, starting with field work, continuing with plant analyses, enclosure

Table 5 Effect of tannins reported in 9 of 54 studies based on laboratory experiments (L) or field experiments (F)

Compound / Plant	Animal species	Author	Year	L/ F	Result
Tannic acid	*Octogon degus*	Bozinovic et al.	1997	L	No effect
	Grammomys dolichurus; *Acomys cahirinus*	Fanson et al.	2008	F	No effect
	Mus musculus	Freeland and Saladin	1989	L	No effect
	Sciurus niger, *Sciurus carolinensis*	Schmidt et al.	1998	F	Middle deterrent effect
	Sciurus carolinensis	Barthelmess	2001	F	Concentration dependent negative effect
	Microtus pennsylvanicus	Bergeron and Jodoin	1991	L	No effect
	Octogon degus, *Phyllotis darwini*	Bozinovic	1997	L	Repellent effect*
Quercus crispula	*Apodemus speciosus*	Takahashi and Shimada	2008	L	Experience dependent negative effect
Several plants	*Microtus oeconomus*	Dai et al.	2014	L	No effect

* to a experimental control

trials and finally laboratory feeding trials to examine differences in plant-animal relationships.

Caveats - Feeding Behavior and Impact on Efficacy Among mammalian herbivores are specialists that feed on a single host plant or on a limited number of species, and generalists that can feed on various plant species. Therefore, it is perhaps easier to find plant-derived repellents against specialists, as they are restricted to a limited range of food by nature. For a generalist, however, it is more difficult to find plant-derived repellents, as they are exposed to a range of PSMs and therefore may be adapted to possible repellents.

Additionally, sensitivity to odors differs among rodent species (Apfelbach et al. 2005) and other herbivorous mammals, e.g., black-tailed deer [*Odocoileus hemionus* (Rice and Church 1974)], is of coures is mirrored in differences in food choice. Another aspect that must be considered in examining foraging behavior is the different food requirements of females and males. Food quality and quantity have a stronger influence on feeding strategies of females (Ostfeld and Canham 1995), and pregnant or lactating females that have higher energetic demands (Jacob et al. 2006). Thus, effects of food quality on reproductive output and hence fitness are more pronounced than in males. However, in the establishment of new infestations, males play a major role because particularly juvenile males disperse in search of new territories and resources (DelBarco-Trillo et al. 2011).

Which Plant Secondary Metabolite Groups Have Potential as Rodent Repellents?

The most promising groups, which may act across rodent species, are the essential oils and terpenoids. Effective pre-ingestive repellent properties have been identified (e.g., for pine needle oil, terpenoides) that repel pocket gophers, voles, red tree voles (*Arborimus longicaudus*), and house mice (Table 2). As already stated above, these pre-ingestive effects are due to their volatility resulting in characteristic deterrent odors.

The complex olfactory system of rodents is important and used in foraging, predator avoidance, and social interactions (Howard and Marsh 1970). In mammals, two olfactory pathways are influenced by odor. The direct route triggers immediate feeding behavior through avoidance, (Hansen et al. 2015, 2016), and the indirect route acts through endocrine activity via the central nervous system e.g., as pheromones that inhibit reproduction (Stowers and Liberles 2016). Compounds should be preferred that affect the behavior of rodents directly.

Species-specific compounds and mixtures include for example: Quinolizidine alkaloids (QA) in agoutis (Guimarães et al. 2003) and dihydroxymethyldihydroxypyrrolidine (DMDP) together with several flavonoids in pocket mice (Janzen et al. 1990); two flavonoids, kaempferol-3-O-β-glucoside and quercetin-3-O-β-glucoside, in Sprague-Dawley rats (Halaweish et al. 2003); oxalic acid in African rodents (Fanson et al. 2008) and squirrels (Schmidt et al. 1998); and glucosinolates in African spiny mice (Samuni-Blank et al. 2013a).

Alkylamides from the fruit of *Xanthoxylum* produce a strong tingling sensation in the mouth and work as a feeding repellent through taste. Cinnamamide, a synthetic derivative of cinnamic acid, is known as a post-ingestive repellent for birds and mammals (Gill et al. 1995) as well as slugs (Watkins et al. 1996). Further investigations on the deterrent effects of the "phenolics group" seem promising, especially low molecular specific phenolics (Cheynier et al. 2013; Virjamo et al. 2013), which are easily extracted from plant material. Their mode of action is via taste and hence, the compounds have to be eaten. As post-ingestive compounds they are suitable for rodent management only in situations where some damage is acceptable. Additionally, they also may negatively affect non-target species when consumed and lead to death (post-absorptive effect) similar to rodenticides (Geduhn et al. 2014).

There are other PSM groups that are part of plant defense mechanisms but were not detected in our literature review. For example, non-protein amino acids are known for their repellent effect on non-specialist herbivores often have deleterious effects on many animals (Bennett and Wallsgrove 1994; Levin 1976). Cyanide and cyanogenic glycosides have acute toxic as well as chronic effects and lead to the death of non-adapted animals (Seigler 1991). Coumarins and furanocoumarins occur in many plants and are toxic in low concentrations to rodents (Berenbaum 1991) and all other warm-blooded organisms. This group already is known in rodent management, because their derivates are used for anticoagulant rodenticides that inhibit blood coagulation (Rosenthal and Berenbaum 1991; Valchev et al. 2008).

When comparing the most promising rodent PSM groups found in the literature to other classes of pest species considerable overlap becomes apparent. Worldwide, insect pests are responsible for pre-harvest loss of 8–15 % of wheat, rice, maize, potato, soybean, and cotton (Oerke 2006) and for up to 10–40 % of food grains loss in granaries and storehouses (Upadhyay and Ahmad 2011). In their review of PSM-based insecticides, Adeyemi (2010) highlighted several potent anti-feedants, with various essential oils and terpenoids showing strong repelling characteristics as in rodents. The methodological approaches and problems are similar to those of rodent researchers who are struggling with the implementation of products for commercial use. These often are hindered by interspecific differences in compound efficacy, environmental pollution, negative effects on ton-target organisms, and costs of application. There are more registered products with natural active ingredients against insects available (see Nerio et al. 2010) than against rodents.

Commercial Products

Despite the extensive literature concerning PSMs for repelling rodents, there are just a few commercial products. Only cinnamon, methyl nonyl ketone (MNK), and pepper oil are available commercially. The registration of these compounds is based partially on the knowledge generated by studies mentioned in this review. Curcumol and triptolide are registered as plant source steriliants for rodent management in China (Huang 2014). Only one rodent repellent based on extracts from hot pepper (*Capsicum annuum*) is registered in China (Z. Zhang, personal communication). In Australia, two plant based products are registered as rodent repellents, i.e., 1. a mixture of white pepper (food flavor) and garlic oil (oil-plant extract), and 2. a mixture of corn mint oil, campher white oil, eucalyptus oil (all oil-plant extracts), and methyl salicylate (phenolic) (https://portal.apvma.gov.au; accessed 12 January 2016). Garbage bags are treated with the latter mixture to repel rodents. The latter mixture also is approved by the USA EPA, which also has authorized the use of products based on capsaicin (derivatives) and on balsam fir oil that is marketed as a botanical rodent repellent (npic.orst.edu/NPRO/;accessed 12 January 2016). Further products (exempt from registration) are available in the USA that are based on white pepper, capsaicin (DeTour for Rodents 2016), garlic, cinnamon, clove, white pepper, rosemary, thyme, peppermint (Nature's defense 2010), castor oil, rosemary oil, mint oil, garlic oil (Thorp 2011), and habañero peppers (Etscorn and Torres 1997).

In the EU, eight repellent or attractant compounds are registered for *biocidal use* against several vertebrate species (European Chemicals Agency's database; accessed 12 January 2016). One of them is methyl nonyl ketone – one of the few PSMs that has been shown to repel rodents under field conditions (Fischer et al. 2013b). However, no product has been registered specifically for rodent use based on this compound and hence no plant based repellent is available for rodents for biocidal use. In the EU plant protection sector, 20 repellent actives are authorized. Four are plant based (clover oil, garlic extract, methyl nonyl ketone, pepper) (EU Pesticides database; accessed 12 January 2016). None of the supported uses by the authorization of these compounds, however, covers rodents, but garlic extract and methyl nonyl ketone are registered for European rabbit (*Oryctolagus cuniculus*) management.

Few repellents are available to effectively minimize rodent damage compared to the variety of rodenticidal compounds and products registered worldwide for rodent management to protect crops and health (Jacob and Buckle 2016). Compared to the number of PSM-based rodent repellent products registered in China, Australia, the USA, and the EU, the number of rodenticidal products authorized is about 300 times higher. As stated above, in the EU there is no PSM-based product registered for repelling rodents, but >3000 rodentical products are authorized (this includes multiple registrations of some products in several member states; according to ECHA Database; accessed 1 March 2016). In the EU, efficacy of biocidal rodenticidal products has to be demonstrated by the applicant to the competent authority of the member state where registration is sought, and must accord to EU Biocides Regulation 528/2012.

Applications - Directions for Further Research

There are many plant metabolites that have been tested under laboratory conditions and found to be efficacious in rodents but have not been translated into commercial products. Many factors must be considered in the decision to develop and market a repellent for rodent management. First, the efficacy under natural conditions (e.g., in the field) must be proven for the target species. Second, the toxicological and environmental properties for the range of concentrations must be considered. The natural origin of a plant-derived compound does not ensure that it is environmentally safe. In many cases, risk assessment must be conducted for potential PSM rodent repellents similar to the risk assessment mandatory for pesticides. Third, application must fit the target species requirements. Production, be it via chemical synthesis or by extraction from plants needs to be cost-effective. In contrast to rodenticides, some volatile compounds and mixtures can act via odor without compounds entering the food chain. Potential negative impact on the environment can be minimized by the application of volatile PSMs via dispensers, thus possibly avoiding direct contact with soil and water bodies.

From a practical point of view, the application of volatile compounds seems promising on a small-scale in confined spaces, such as storage facilities because evaporation of volatile substances can have a strong effect on rodents (Epple et al. 1996; Fischer et al. 2013a; Hansen et al. 2015, 2016). One disadvantage of essential oils and terpenoids is their high volatility. Dilution of the gas phase of the compound soon after application can result in a reduced effect. Research is needed to improve stability of formulations to ensure long-lasting emission of volatiles.

The use of plant-derived repellents for large-scale field application seems challenging to implement, and will require different application strategies. One option is the use of drip irrigation to apply repellents similar to the application of pesticides (Ghidiu et al. 2012). As for other management tools, it needs to be demonstrated that benefits in terms of damage prevention outweigh the cost of management.

Summary

Our review indicates that PSMs can repel several rodent species. There is potential for use as a tool for rodent management in several situations. These include reducing damage to crops in fields and to grain in storage facilities. In many cases, there has been no translation of the results of the testing of metabolites for repelling rodents from laboratory cage to enclosure and field studies. Often, the efficacy found in cage trials cannot be repeated in enclosure or field trials. This lack of successful transitions from laboratory to field applications is the likely reason why there are only a small number of PSM-based repellents registered for rodent management worldwide.

Promising groups of rodent repellents are essential oils and terpenoids, because they operate pre-ingestively and can act across species. Cinnamamide (phenolics) and alkylamides also have potential, but they act post-ingestively and some crop damage will occur before aversion sets in. Other compounds and mixtures appear to be species-specific, which provides the opportunity to focus management on a particular target species and to minimize unwanted non-target effects. Potential uses of PSMs include the protection of crops and storage facilities by repelling rodents and the use of attractive odors that lure them away to other habitats (push-and-pull strategy). Attractants are also useful for improving trap success, or to enhance bait acceptance (Shumake and Hakim 2000). A few studies suggest that PSM odors have reproductive effects (Tran and Hinds 2012). Effects of PSMs in rodents can contribute to an ecological friendly rodent pest management system as they can be used as an addition to an integrated rodent management tool box. Currently, there is neither a general approach for the study of PSMs as rodent repellents nor a harmonized protocol for identifying rodent repellent effects among species. Field use of PSMs should be preceded by detailed laboratory work that elucidates the mechanistic relationship between a compound and rodent response, thus enabling an appropriate application. Repelling individuals from a target (e.g., a valuable plant or a certain area) will inevitably turn them to alternative food sources in surrounding areas. This response needs to be incorporated into potential application schemes.

Although there has been significant progress in the identification of the functional mechanisms that cause effects of natural products on rodent behavior research needs to be expanded before being utilized on a broad scale for management purposes. Among the challenges are achieving sustainable efficacy, preventing unwanted environmental effects, and basic economical considerations. However, a rigorous stepwise approach (cage, enclosure, field trials) that concentrates on the most promising PSM groups may increase the likelihood of identifying effective and safe metabolites, and the development of a range of repellent products for crop and hygiene protection from rodents.

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