Almuth Hammerbacher (ORCID: 0000-0002-0262-2634)

Teresa A. Coutinho (ORCID: 0000-0002-3227-4343)

Jonathan Gershenzon (ORCID: 0000-0002-1812-1551)

Title: **Roles of plant volatiles in defense against microbial pathogens and microbial exploitation of volatiles**

Authors: Almuth Hammerbacher[1], Teresa A. Coutinho[2] and Jonathan Gershenzon[3]

Author affiliations: [1]Department of Zoology and Entomology, Forestry and Agricultural Biotechnology Institute, University of Pretoria, Pretoria, South Africa

[2]Department of Biochemistry, Genetics and Microbiology, Forestry and Agricultural Biotechnology Institute, Centre for Microbial Ecology and Genetics, University of Pretoria, Pretoria, South Africa

[3]Department of Biochemistry, Max Planck Institute for Chemical Ecology, Hans-Knoell Str 8, 07745 Jena, Germany

Corresponding author: Almuth Hammerbacher (almuth.hammerbacher@fabi.up.ac.za)

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Running title: Are plant volatiles anti-microbial defenses?

Abstract

Plants emit a large variety of volatile organic compounds during infection by pathogenic microbes, including terpenes, aromatics, nitrogen-containing compounds, fatty acid derivatives, as well as the volatile plant hormones, methyl jasmonate and methyl salicylate. Given the general anti-microbial activity of plant volatiles and the timing of emission following infection, these compounds have often been assumed to function in defense against pathogens without much solid evidence. In this review we critically evaluate current knowledge on the toxicity of volatiles to fungi, bacteria and viruses and their role in plant resistance as well as how they act to induce systemic resistance in uninfected parts of the plant and in neighboring plants. We also discuss how microbes can detoxify plant volatiles and exploit them as nutrients, attractants for insect vectors, and inducers of volatile emissions that stimulate immune responses that make plants more susceptible to infection. Although much more is known on plant volatile-herbivore interactions, knowledge of volatile-microbe interactions is growing and it may eventually be possible to harness plant volatiles to reduce disease in agriculture and forestry. Future research in this field can be facilitated by making use of the analytical and molecular tools generated by the prolific research on plant-herbivore interactions.

Keywords: terpenes, green leaf volatiles, aromatic volatiles, direct defense, systemic induced resistance, detoxification, insect vectors

1. Introduction

Plants produce and emit a large variety of volatile organic compounds that have an impact on other organisms. These compounds are often produced in the epidermal cell layer, which facilitates easy volatilization through the cell membrane and wall at the plant-air interface (Dudareva, Pichersky & Gershenzon, 2004; Kolosova, Sherman, Karlson, & Dudareva, 2001). Alternatively, volatiles are stored in secretory structures, such as glandular trichomes, secretory cavities and resin ducts, as lipophilic secretions that are released upon mechanical damage and become volatiles when in contact with air due to their low vapor pressures (Gershenzon, Maffei, & Croteau, 1989; Martin, Gershenzon, & Bohlmann, 2003) or when actively transported to the surface (Adebesin et al., 2017). Plant emission of volatile blends is often precisely timed and localized, but their biological functions are still elusive in many cases despite intensive investigations (Pichersky & Gershenzon, 2002; Dudareva et al., 2004).

Some volatiles are known to play critical physiological roles to alleviate oxidative stress induced by high light intensity by functioning as scavengers of reactive oxygen species, membrane stabilizers, or as regulators of stress responses (Sharkey & Yeh, 2001; Zuo et al., 2019). In addition, volatiles emitted by flowers attract pollinators for angiosperm reproduction (Dudareva, Klempien, Muhlemann & Kaplan, 2013), while volatiles from fruits attract frugivores that disperse seeds (Pichersky & Gershenzon, 2002). Plant volatiles also facilitate intra- or inter-plant communication by signaling information about an impending danger either to distant parts of the same plant or to neighboring plants (Karban, Shiojiri, Huntzinger, & McCall, 2006). Furthermore, plants emit volatiles in response to feeding damage by herbivores (Dudareva et al., 2013; Pichersky & Gershenzon, 2002); these can either act as direct defenses by intoxicating the herbivore or as indirect defenses by revealing the location of the herbivore to predators and parasitoids of the third trophic level (Turlings & Erb, 2018).

Volatiles could also function to prevent microbial attack, but little research has been carried out on this topic in comparison to the other proposed roles. Volatile chemical compounds extracted from plants, known as essential oils, have been studied since antiquity for their anti-microbial activities and are still popular subjects for biomedical research today (Radulovic, Blagojevic, Stojanovic-Radic & Stojanovic, 2013). Yet how volatiles protect against infection by phytopathogenic fungi, bacteria and viruses is poorly documented. In this review we first introduce the major groups of plant volatiles and their biosynthetic pathways. Next we critically evaluate current knowledge on plant volatiles as direct defenses against microbes and as signals that trigger defense responses. Finally, we describe how microbes can detoxify plant volatiles and use them for their own benefit as nutrients and attractants for insect vectors.

2. Plant volatiles belong to different chemical classes with diverse biosynthetic origins

Plant volatiles can be classified into different types based on their chemical structures and biosynthetic pathways (Figure 1). The largest known group of volatiles is the terpenes. These compounds are often stored in secretory structures, including resin ducts (Martin et al., 2003), secretory cavities (Heskes, Lincoln, Goodger, Woodrow & Smith, 2012), secretory idioblasts (Bakker & Gerritsen, 1990) or glandular trichomes (Gershenzon et al., 1989) as constitutive defenses against attackers. However, they can also be produced *de novo* following an external stimulus, such as wounding (Turlings and Erb, 2018). The monoterpenes are largely synthesized by the methylerythritol phosphate pathway (MEP pathway) which is localized in the chloroplasts (Phillips, Leon, Boronat & Rodriguez-Concepcion, 2008). Sesquiterpenes, on the other hand, are synthesized

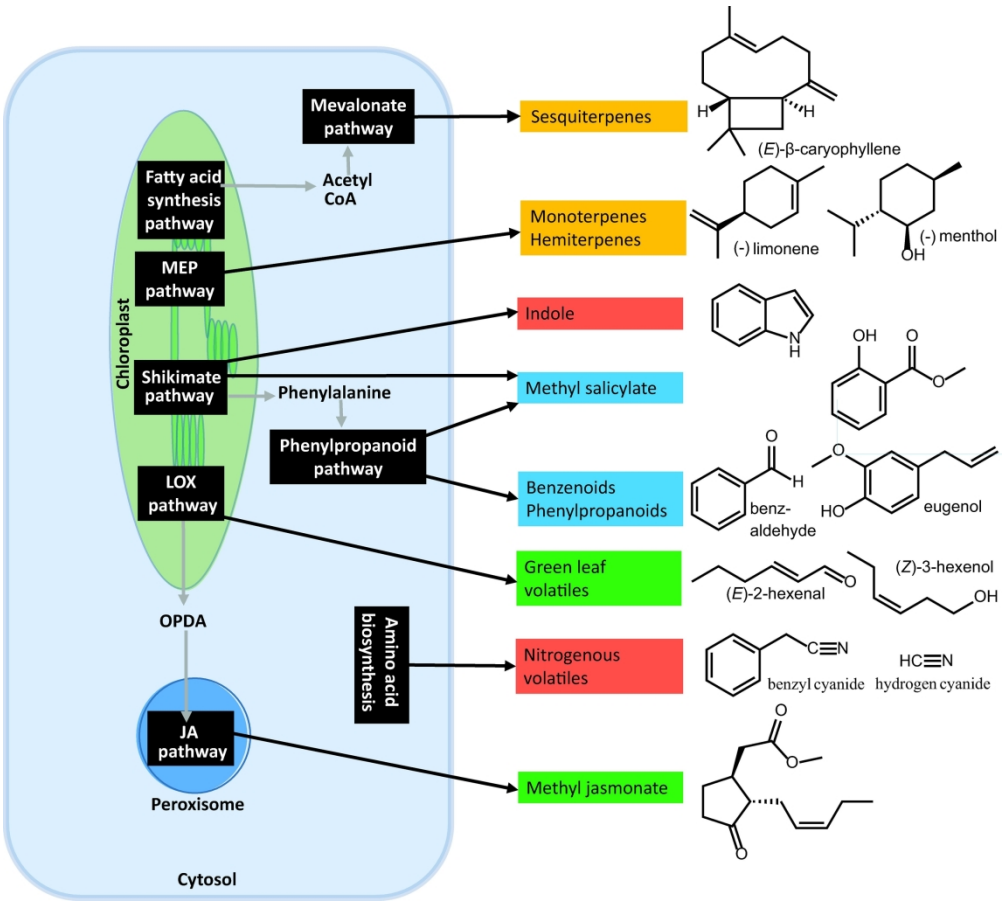

Figure 1: Volatile biosynthesis pathways in plants produce a wide variety of different compounds. Terpenes (yellow), nitrogen-containing compounds (red), aromatic volatiles (blue) and derivatives of the lipoxygenase pathway (green) are produced in different compartments within the plant cell. MEP: methylerythritol phosphate; CoA: coenzyme A; LOX: lipoxygenase; JA: jasmonic acid

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through the mevalonate pathway (MVA pathway) in the cytosol. The end-products of both pathways are the C_5 isoprenoids, isopentenyl diphosphate (IDP) and dimethylallyl diphosphate (DMADP). In the later steps of terpene biosynthesis, IDP and DMADP are coupled by isoprenyl diphosphate synthases to form neryl or geranyl diphosphate, C_{10} compounds, or various isomers of farnesyl diphosphate (C_{15}), which serve as the substrates for monoterpene or sesquiterpene synthase enzymes, respectively (Dudareva et al., 2013; Sallaud et al., 2009; Schilmiller et al., 2009). A large variety of monoterpene and sesquiterpene synthases are known and have been characterized in many different plant species (Arimura, Huber & Bohlmann, 2004; Degenhardt, Köllner & Gershenzon, 2009; Martin et al., 2003). The activity of these enzymes is often, but not exclusively regulated on a transcriptional level to ensure timely emission of volatiles following an external stimulus, such as herbivory, or during a developmental stage, such as flowering or the early growth periods of young leaves (Arimura et al., 2004; van Schie, Haring and Schuurink, 2006). *De novo* terpene synthesis is stimulated by plant defense hormones, including salicylic acid (a plant hormone regulating defense responses to biotrophic attack, e. g. by aphids or rust fungi) (Eberl, Hammerbacher, Gershenzon & Unsicker, 2018) and jasmonic acid (a plant hormone regulating defense responses against necrotrophic attack e. g. insect feeding or infection by *Botrytis cinerea*) and ethylene (Arimura et al., 2004; Martin et al., 2003).

Benzenoids and phenylpropanoids (Figure 1) are produced in most plants from the amino acid phenylalanine (Dudareva & Pichersky, 2006; Pichersky & Gershenzon, 2002) which is deaminated by phenylalanine ammonia lyase to form *trans*-cinnamic acid, which can be transformed to various C_6-C_1 benzenoid compounds via a β-oxidative or a non-β-oxidative pathway (D'Auria, Chen & Pitchersky, 2003; Dudareva et al., 2013). Alternatively, *trans*-cinnamic acid is transformed by the monolignol biosynthesis pathway to the precursors of softwood lignin, coumaryl- and coniferyl alcohol, before being reduced, acetylated and methylated to form volatile C_6-C_3 compounds (Dudareva et al., 2013). The formation of volatile benzenoids and phenylpropanoids in plants is often linked to specific developmental processes, such as flowering, or formation of secretory structures in young leaves (Dudareva & Pichersky, 2006; Pichersky & Gershenzon, 2002). Methyl-salicylate, on the other hand, serves as a mobile signal for inducing systemic resistance after attack by biotrophic organisms (Dempsey, Vlot, Wildermuth & Klessig, 2011)and is derived in some plants directly from the shikimate pathway in the plastids.

Nitrogen-containing volatiles (Figure 1) have diverse origins in the plant cell. For example, indole is a precursor of tryptophan biosynthesis and is emitted from plants, such as maize, after herbivore feeding (Gierl & Frey, 2001). Volatile aldoximes and nitriles derived from amino acids are emitted by plants upon herbivore damage serving as direct as well as indirect defenses (Irmisch et al., 2013;

2014). On the other hand, many toxic nitrogen-containing volatiles are only produced after hydrolysis of a non-volatile glycosylated precursor that is itself non-toxic. Well-known examples are the glucosinolates of the Brassicaceae (Kliebenstein, Kroymann, & Mitchell-Olds, 2005) and the cyanogenic glycosides produced in many different plant species, including cassava and rubber (Poulton, 1990). Plants producing these secondary metabolites also produce a glucosidase enzyme that is sequestered separately from the non-toxic precursor or pro-toxin. When this strict compartmentalization is breached by, for example, tissue disruption due to herbivory or pathogen infection, the glucosidase hydrolyses the pro-toxin to release an unstable intermediate, which rearranges to form a toxic volatile (Kliebenstein et al., 2005; Poulton, 1990).

Volatile fatty acid derivatives (Figure 1) include the green leaf volatiles (GLVs) as well as methyl jasmonate, both of which are produced through the lipoxygenase (LOX) pathway (Ameye et al., 2018; Matsui, 2006). In this pathway, the C_{18} unsaturated fatty acids, linoleic acid and linolenic acid, undergo stereospecific oxidation to form hydroperoxy-intermediates. For the biosynthesis of GLVs, these intermediates are cleaved to form C_6 and C_9 unsaturated volatile aldehydes that can be further reduced to alcohols and then acetylated (Ameye et al., 2018; Matsui et al., 2006). Methyl jasmonate, on the other hand, is synthesized in the peroxisome from a 13-hydroperoxide intermediate via sequential β-oxidation (Dudareva et al., 2013). All of these volatile fatty acid derivatives are produced in response to herbivory or attack by necrotrophic pathogens, and both GLVs and methyl jasmonate are thought to regulate each other's synthesis via a positive feed-back loop (Ameye et al., 2018; Scala, Allmann, Mirabella, Haring & Schuurink, 2013[a]).

3. Volatiles can function as direct defenses against plant pathogenic microbes or as signals for anti-microbial responses

3.1. Volatiles as direct anti-microbial defenses

Throughout much of human history the anti-microbial activities of plant volatiles have been well known. These substances formed an integral part of the pharmacopeia of the ancient Egyptians, Greeks and most other cultures. Essential oils are still used in Western homeopathic, traditional Chinese and Ayurvedic medicine to heal infections, and modern medicine has been studying the anti-microbial effects of volatile plant metabolites to find therapeutic drugs for common human pathogens, especially against those microbes that have evolved multi-drug resistance (Dima & Dima, 2015).

For this reason, the anti-microbial modes of action of many volatiles are well studied. Most are believed to act on bacterial and fungal membranes, influencing their integrity and permeability

(Sikkema, de Bont & Poolman, 1995). For example, terpenes are known to damage cell membranes by integrating between the acyl chains of phospholipids causing leakage of ions and metabolites, such as ATP (Lambert, Skandamis, Coote, & Nychas, 2001). The aromatic volatiles, especially the phenylpropanoids, are reported to bind to proteins in the cell membranes, thereby changing their conformation (Bennis, Chami, Chami, Bouchikhi, & Remmal, 2004). Similarly, GLVs, such as (*E*)-2-hexenal bind to microbial proteins secreted into the extracellular space, rendering them non-functional (Myung, Hamilton-Kemp, & Archbold, 2007), whereas indolic volatiles are known to disrupt the integrity of the cytoskeleton (Mei et al., 2019). In addition, plant volatiles can cause programmed cell death (Chen et al., 2014), disrupt the respiratory electron chain (Fry & Munch, 1975) inhibit specific enzymes (Wendakoon & Sakaguchi, 1995) and interrupt communication between microbial cells such as that in bacterial quorum sensing (Joshi et al., 2016). It is interesting to note, that while there is a wealth of information on the *in vitro* effects of volatiles on microbes, especially on human pathogens, little is known about their effects on plant pathogens *in vivo,* although plants emit a broad diversity of volatiles during infection by fungi and bacteria (Attaran, Rostás, & Zeier, 2008; Sharifi, Lee & Ryu, 2018).

De novo synthesis of volatile terpenes is frequently induced upon pathogen infection in numerous plant species. For example, a susceptible poplar cultivar infected by the rust fungus, *Melampsora larici-populina*, emitted higher levels of terpenes compared to healthy plants (Eberl et al., 2018). However, in this case as in most other infection-induced volatiles, it is still unknown if emissions affect the invading pathogen positively or negatively. In *Arabidopsis*, emission of the homoterpene (*E,E*)-4,8,12,11-tridecatetraene during infection by *Pseudomonas syringae* had no negative effects on the bacterium. Furthermore, it is thought that this homoterpene might even provide a fitness benefit to the pathogen since its formation is induced by jasmonic acid signaling, which arises as a result of pathogen manipulation of the plant (Attaran et al., 2008).

On the other hand, a number of studies report positive correlations between plant volatile emission and resistance to pathogens (Table 1). For example, downy mildew (*Plasmopara viticola*) resistant grapevine genotypes emitted significantly more mono- and sesquiterpenes than susceptible genotypes (Algarra-Alarcon et al., 2015). Rice genotypes with resistance against a bacterial pathogen, *Xanthomonas oryzae* pv. *oryzae*, were shown to emit large quantities of either the sesquiterpene, (*E*)-nerolidol, or the monoterpene, (-)-limonene (Kiryu et al., 2018; Lee, Chung, Kang, Chung & Lee, 2016). Both compounds were toxic to the bacterium at physiologically relevant concentrations *in vitro* (Kiryu et al., 2018; Lee et al., 2016). In citrus, higher emissions of C_6 aldehydes (GLVs) and monoterpenes also correlated with plant tolerance to huanglongbing disease (Hijaz, Nehela & Killiny, 2016).

Table 1: Volatiles with *in vivo* activities in direct and indirect defense against bacterial and fungal pathogens

Host plant	Pathogen	Pathogen lifestyle	Emitted volatile	Activity*	Citation
Arabidopsis thaliana ecotype Columbia	*P. syringae pv. tomato*	Hemibiotrophic	(*E*)-2-hexenal	Decreased resistance in the emitting plant	Scala *et al*., 2013
			α and β-pinene	Increased resistance in the emitting and neighbouring plants	Riedlmeier *et al*., 2017
			(*E,E*)-4,8,12,11-tridecatetraene	No effect.	Attaran *et al*., 2008
			(*E*)-β-caryophyllene	Increased resistance in the emitting plant's flowers	Huang *et al*., 2012
	Botrytis cinerea		C_6-aldehyde GLVs	Increased resistance in the emitting plant	Shiojiri *et al*., 2006
			C_6-aldehyde GLVs	Increased resistance after aerial application	Bate and Rothstein, 1998; Kishimoto *et al*., 2005; 2006; 2008
Solanum lycopersicum	*P. syringae pv. tomato*	Hemibiotrophic	esters of (*Z*)-3-hexenol	Increased resistance in the emitting plant	Lopez-Gresna *et al*., 2018
	Alternaria alternata pv. lycopersici	Necrotrophic	GLVs	Increased resistance in the emitting plant	Xin *et al*. 2014
Oryza sativa	*Xanthomonas oryzae pv. oryzae*	Hemibiotrophic	(*E*)-nerolidol	Increased resistance in the emitting plant	Kiryu *et al*., 2018
			(-)-limonene	Increased resistance in the emitting plant	Lee *et al*., 2016
			GLVs	Decreased resistance in the emitting plant	Tong *et al*., 2012
	Magnaporthe oryzae	Necrotrophic	(-)-limonene	Increased resistance in the emitting plant	Chen *et al*., 2018
			indole	Increased resistance in the emitting plant	Shen *et al*., 2018
Phaesiolus spp.	*P. syringae pv. syringae*	Hemibiotrophic	nonanal	Increased resistance in the emitting and neighbouring plants	Yi *et al*., 2009
	Colletotrichum lindemuthianum	Necrotrophic	terpenes and GLVs	Increased resistance in the emitting and neighbouring plants	Quitana-Rodriguez *et al*., 2015
Zea mays	*Aspergillus flavus*	Necrotrophic	(*Z*)-hexenal and (*Z*)-decanal	Increased resistance in the emitting plant	Zeringue *et al*., 1996
	Fusarium spp.	Hemibiotrophic	indole	Increased resistance in the emitting plant	Shen *et al*., 2018
Triticum aestivum	*Fusarium graminearum*	Hemibiotrophic	(*Z*)-3-hexenyl acetate	Increased resistance after aerial application	Ameye *et al*., 2015
Vitis vinifera	*Plasmopara viticola*	Biotrophic	mono-and sesquiterpenes	Increased resistance in the emitting plant	Algarra-Alarcon *et al*., 2015
Allium sativum	*Sclerotium cepivorum*	Necrotrophic	mono-and sesquiterpenes	Increased resistance in the emitting plant	Pontin *et al*., 2015
Citrus sinensis	*Candidatus* Liberibacter asiaticus	Biotrophic	terpenes and GLVs	Increased resistance in the emitting plant	Hijaz *et al*., 2016
Malus domestica	*Erwinia amylovora*	Hemibiotrophic	Methyl salicylate	Vector deterrent	Cellini *et al*., 2018

* Methyl jasmonate and salicylate are excluded from this table

Other evidence for a role of terpenes in plant defense against microbes comes from garlic where the terpenes produced upon infection by *Sclerotium cepivorum* had fungistatic effects at the emitted concentrations (Pontin, Bottini, Burba, & Piccoli, 2015). Meanwhile, in rice, a cultivar producing higher levels of (-) limonene during infection by the rice blast fungus, *Mangnaporthe oryzae* (Chen et al., 2018) was found to have a terpene synthase producing (-)-limonene, which was highly expressed during infection. Genetically modified rice plants, overexpressing this gene, were substantially more resistant against *M. oryzae* than wild-type plants and plants in which the expression of this gene was silenced by RNA interference (Chen et al., 2018). This study therefore provided some evidence that (-)-limonene is an anti-microbial defense with *in planta* activity, although in all of these cases volatile emission by plants might just coincide with the presence of other defenses, which provide the host with actual protection against the pathogen.

Green-leaf volatiles (GLVs) are emitted from leaves after infection by plant pathogens, such as *P. syringae, Botrytis cinerea* or *Colletotrichum* sp (Table 1). These compounds might function in defense since the C_6 aldehydes and alcohols especially have strong anti-microbial effects *in vitro* against bacteria (Croft, Juttner, & Slusarenko, 1993) or fungi (Matsui et al., 2006; Prost et al., 2005) at physiologically relevant concentrations. However, the *in vivo* effects of these compounds were sometimes shown to promote pathogen infection. For example, *Arabidopsis* producing higher levels of GLVs was more susceptible to *P. syringae* pv. *tomato* (Scala et al., 2013[b]) and rice with genetically impaired GLV biosynthesis was more resistant to *X. oryzae* pv. *oryzae* (Tong et al., 2012). These findings were explained by the fact that the biosynthesis of GLVs is co-regulated with jasmonate-related signal transduction. Jamonate is known to be a strong antagonist of salicylic acid-dependent signaling in some herbaceous species, which is important for plant defenses against biotrophic pathogens. It is thought that biotrophic and hemibiotrophic pathogens, such as *P. syringae* and *X. oryzae* benefit from GLV emissions due to a jasmonate-mediated down-regulation of the infected plant's salicylic acid-dependent defense mechanisms (Scala et al., 2013[b]).

On the other hand, necrotrophic fungal pathogens seem to be negatively affected by GLV emissions, as jasmonate-mediated signaling cascades that trigger effective defense responses against these pathogens also trigger GLV emission (Table 1). In addition, GLVs were shown to directly affect some fungal pathogens *in vivo*. As with the terpenoids, a number of studies showed positive correlations between GLV emission and pathogen resistance. For example, a positive correlation between resistance to *Aspergillus flavus* infection and (*Z*)-hexenal and (*Z*)-decenal was shown in maize kernels (Zeringue, Brown, Neucere & Cleveland, 1996). Furthermore, exposure of *Colletotrichum lindemuthianum* spores to the head-space volatiles of a resistant bean genotype producing high levels of nonanal and other volatiles, irreversibly inhibited spore germination

(Quitana-Rodriguez et al., 2015). *In vivo* evidence, based on a functional genetics approach, showed that these compounds can be directly toxic to pathogens during the infection process, as well. For example, transgenic tomato or *Arabidopsis* plants over-producing GLVs were significantly more resistant to *Alternaria altenata* f. sp. *lycopersici* (Xin, Zhang, Zhang, Chen & Sun, 2014) or *B. cinerea* (Kishimoto, Matsui, Ozawa & Takabayashi, 2008; Shiojiri et al., 2006), respectively, compared to wild type plants.

Over 1700 floral volatiles have been identified (Muhlemann et al., 2014) in 90 different angiosperm and gymnosperm families (Knudsen et al. 2006). Compared to other plant parts, flowers release the highest amount and largest diversity of volatiles (Muhlemann et al., 2014). The primary functions of floral volatiles are to attract pollinators and defend against florivores and pathogens. Pollinator attraction is thought to be mostly mediated by benzenoids, whereas defense functions are facilitated by both terpenoids and benzenoids (Schiestl, 2010). Pollen and nectar are attractive to both pollinating and non-pollinating insects as well as to microbes. Microbes in flowers, however, can have a negative impact on plant reproductive fitness by either destroying floral tissue or by disrupting pollination in other ways (McCall & Irwin, 2006; Junker & Bluthgen, 2010; Junker, Romeike, Keller & Langen, 2014). For example, bacteria residing in flowers have sometimes been shown to degrade nectar sugars and alter nectar pH (Vannette et al. 2013). Volatiles have been well documented to defend flowers against florivores such as ants, beetles and other insects (Junker & Bluthgen, 2008; Willmer et al., 2009). Floral volatiles also exhibit antibacterial and antifungal activities *in vitro* (Bakkali, Averbeck, Averbeck & Idaomar, 2008; Junker & Tholl, 2013) and thus it is not surprising that they have sometimes demonstrated a role in plant defense against pathogens and other microbes residing in and on the flower tissue. For example, (*E*)-β-caryophyllene emitted from the stigmas of *Arabidopsis* flowers was shown to inhibit growth of the pathogen *P. syringae* pv. *tomato* (Huang et al., 2012). Similarly, the diversity of bacterial epiphytes on leaves and petals of *Saponaria officinalis* and *Lotus corniculatus* was shown to be much lower on petals, possibly due to the antibacterial function of the floral scents (Junker et al., 2011). (*S*)-(+)-Linalool, one of the most common volatiles emitted by angiosperm flowers (Knudsen et al., 2006), which has antimicrobial properties (Queiroga et al., 2007), was shown to defend *Penstemon digitalis* flowers by slowing the growth rate of specific bacteria (Burdon, Junker, Scofield & Parachnowitsch, 2018).

Insect pollinators, during their foraging activities, may sometimes vector plant pathogens (McArt, Koch, Irwin & Adler, 2014). In order to prevent pollinators from spreading a disease from one flower to another, flowers can produce deterrent volatiles. For example, in the case of *Erwinia amylovora*, the causal agent of fireblight on pome fruit trees, honeybee-mediated dispersal has been demonstrated (Johnson, Stockwell, Burgett, Sugar & Lopez, 1993). However, honeybees are

attracted to healthy as opposed to diseased flowers. Cellini et al. (2019) suggested that this discrimination may be due to differential emissions of volatile compounds. For example, methyl salicylate, known to play a significant role in plant defense against biotrophic pathogens, is released by inoculated flowers and appears to repulse the honeybees. The emission of this compound may reduce the spread of infections on trees already inoculated with the fireblight pathogen and even protect neighboring fruit trees from infection.

Taken together, there is strong evidence that plant volatiles possess anti-microbial activity *in vitro*, and that emission is correlated with resistance. However, only scattered reports have demonstrated the direct *in vivo* antimicrobial activities of plant volatiles during microbial host infection and colonization. Thus it is premature to make broad generalizations about the direct role of volatiles in defending plants from pathogen colonization and invasion. More investigation is necessary to define at what stage of the infection process volatiles act, either prior to or after host colonization has taken place. In addition, since plant volatiles are often emitted as complex mixtures, it is important to determine if individual compounds are active or whether the mixture has additive or synergistic effects due perhaps to the different mode of action of components of the mixture.

3.2. Volatiles as signals that induce systemic resistance against pathogens

Two volatile plant defense hormones, methyl salicylate and methyl jasmonate, provide a means for plants to systemically induce defense responses in plant parts distant from the initial site of infection without the necessity of having a signal transit through the vascular system. Repeated applications of methyl salicylate, for example, to uninfected *Nicotiana benthamiana* seedlings resulted in greater protection against *P. syringae* pv. *tabaci* and *Pectobacterium carotovorum* subsp. *carotovorum* compared to untreated control plants (Song & Ryu, 2018). Similar patterns of defense-induction were also shown for plants after methyl jasmonate applications (e. g. Karban et al., 2006; Lundborg, Sampedro, Borg-Karlson & Zas, 2019). Volatile signals can also travel between plants if they are close enough together (Karban et al., 2006; Heil & Karban, 2010). For example, methyl salicylate released from tobacco plants infected with *tobacco mosaic virus* caused the reduction of viral infection symptoms in neighboring plants (Shulaev, Silverman & Raskin, 1997). Thus, volatile methyl jasmonate and methyl salicylate released by plants are likely to induce systemic resistance against pathogens when perceived by as yet uninfected organs or neighboring plants. It can be expected that methyl jasmonate targets necrotrophic plant pathogens and methyl salicylate targets biotrophic pathogens, consistent with the roles of their corresponding non-volatile analogs, jasmonic acid and salicylic acid.

Systemic resistance can result in the activation of anti-pathogen defenses, or instead can prime the plant against future infection by preparing the defensive system for a faster and/or stronger reaction (Conrath, Beckers, Langenbach & Jaskiewicz, 2015; Mauch-Mani, Baccelli, Luna & Flors, 2017). The primed state can last for the life of the plant and can even be transmitted to its descendants. Interestingly, in a recent study by Bertini, Proietti, Focaracci, Sabatini, & Caruso (2019), it was shown that the mechanism by which a plant is primed to respond faster against future infections is via epigenetic changes, including modifications of histones in promoter regions and DNA methylation patterns. However, the reaction of the primed plant during subsequent challenges depends on the plant-pathogen combination and is probably also influenced by the developmental stage of the host and environmental factors (Balmer, Pastor, Gamir, Flors & Mauch-Mani, 2015).

Apart from the volatile forms of defense hormones, other volatiles can induce a systemic response in other plant organs or in neighboring plants (Table 1). For example, treatment of maize and rice with indole, a volatile commonly emitted by grass species during herbivore damage, induced systemic resistance against pathogens in the treated plants (Shen, Liu, Wang & Wang, 2018). Indole triggered the formation of reactive oxygen species, followed by higher expression of defense-related genes during subsequent challenges with hemibiotrophic and necrotrophic pathogens. Fumigation of *Arabidopsis* with the monoterpenes α- and β-pinene increased expression of genes related to defense against biotrophic pathogens, and here again reactive oxygen species were part of the signaling cascade (Riedlmeier et al., 2017). Interestingly, *Arabidopsis* expressing an inducible *P. syringae* effector protein emitted both α- and β-pinene naturally and neighboring wild type plants that perceived these volatiles showed similar defense responses (Riedelmaier et al., 2017). Similarly, a volatile mixture containing mainly monoterpenes from a *C. lindemuthianum* resistant bean variety could induce systemic resistance in a susceptible bean cultivar to this necrotrophic pathogen (Quintana-Rodriguez et al., 2015).

Numerous studies have shown that GLVs are effective signals in intra- and inter-plant communication during herbivore attack (Heil & Karban, 2010). These volatiles, can also be used by plants to communicate the presence of pathogen infection. Aerial application of C_6-aldehydes such as (*Z*)-3-hexenal to *Arabidopsis* elicited higher expression of defense-related genes in the phenylpropanoid and jasmonate biosynthetic pathways (Bate and Rothstein, 1998; Kishimoto, Matsui, Ozawa & Takabayashi, 2005), as well as an increase in lignification in leaves (Kishimoto, Matsui, Ozawa & Takabayashi, 2006). Such (*Z*)-3-hexenal treated *Arabidopsis* plants were more resistant to infection by the necrotrophic fungus, *B. cinerea*, compared to untreated plants (Kishimoto et al., 2005; 2006). Whereas the C_6-aldehydes were effective in inducing resistance in *Arabidopsis* to a necrotrophic fungal pathogen (Kishimoto et al., 2005; 2006), the C_9-aldehyde,

nonanal, induced resistance in bean plants growing in a natural population to a hemibiotrophic bacterial pathogen (Yi, Heil, Adame-Alvarez, Ballhorn & Ryu, 2009). The authors first induced systemic resistance in specific plants within the population by treating them with a salicylic acid analogue, which increased nonanal emission. Neighboring plants perceiving this volatile aldehyde then became significantly more resistant to *P. syringae* pv. *syringae*.

Volatile acetic, propionic, or butyric esters of GLVs emitted by plants during fungal infection (Ameye et al., 2018) are also signals that cause resistance responses. For example, exposure of wheat plants to (*Z*)-3-hexenyl acetate induced resistance against *Fusarium graminearum*, a hemibiotrophic pathogen (Ameye et al., 2015). This induced resistance was thought to be due to an increase in transcription of jasmonate-responsive genes, targeting the necrotrophic phase of the pathogen. Esters of (*Z*)-3-hexanol were also shown to induce resistance in a variety of crop plants against bacterial infection, and this was due to their eliciting closure of stomata (Lopez-Gresna et al., 2018), a response previously shown to be triggered by salicylic acid and abscisic acid (Melotto, Zhang, Oblessuc & He, 2017). Tomato plants, in which the emission of these volatiles was silenced, were hypersensitive to *P. syringae* pv. *tomato* infection due to slower stomatal responses (Lopez-Gresna et al., 2018).

Volatiles that induce systemic resistance against pathogens, such as GLVs, could be employed in agriculture as 'green vaccines' against impeding pathogen attacks (Luna, 2016). However, knowledge on the mechanisms by which volatiles induce systemic resistance is still in its infancy and it is not known whether broad application would cause significant reduction in plant productivity. Furthermore, there is little information about the receptors for volatiles and the signal cascades required to elicit an appropriate state of defense-readiness. Although much has been learned about the hormone signaling of systemic resistance for specific plant-pathogen combinations (Table 1), no general mechanisms have emerged. For example, GLVs are thought to activate defenses regulated by the jasmonic acid signaling cascade and should therefore induce resistance against necrotrophic pathogens. This has been shown for the fungal pathogen *B. cinerea*, but the data for bacterial pathogens with hemibiotrophic lifestyles are highly conflicting: GLVs increased the susceptibility of *Arabidopsis* to *P. syringae* pv *tomato* (Scala et al., 2013[b]), while these volatiles decreased the susceptibility of tomato or bean plants to the same bacterial pathogen (Lopez-Gresna et al., 2018), or the closely related *P. syringae* pv. *syringae* (Yi et al., 2009), respectively.

Pathogens might also have evolved adaptations to host signals and could themselves influence the outcome of the interaction. For example, *P. syringae* uses the toxin coronatine to activate jasmonate-related defense responses and stimulates the host to increase its GLV emissions (Scala et

al., 2013[b]). Receiver plants upon perceiving these volatiles might therefore activate their jasmonate-driven defense signaling cascade, thereby inadvertently increasing their susceptibility to this pathogen. This response would allow easier spread of the pathogen and could also benefit plants by increasing infection of neighboring plants that are potential competitors. Higher GLV emissions during fungal infections might be caused by fungal effector lipases, which increase the available pool of free fatty acids for GLV biosynthesis (Ameye et al., 2018). Effector lipases have been previously shown to interfere with callose deposition, a well-known anti-fungal defense (Bluemke et al., 2014). To unravel the complexities of volatile signaling and pathogen resistance, individual plant-pathogen combinations must be studied on a case-by-case basis, taking both the host and pathogen responses into account.

4. Microorganisms can circumvent volatile plant defenses and use them for their own advantage

4.1. Detoxification of volatiles and their utilization as nutrient sources

Many (perhaps all) plant pathogens possess traits to counter host defenses. Indeed, there appear to have been numerous cycles involving plant evolution of more effective defenses followed by pathogen counter-adaptation over the course of evolution, as suggested by the large families of pathogen effector and plant resistance genes (e. g. Bluemke et al., 2014). Pathogen traits that circumvent plant defenses can include enzymes catalyzing the detoxification of plant defenses by glycosylation (Pedras, Ahiahonu & Hossain, 2004) or oxidation (Wang et al., 2014), use of defense compounds as nutrient sources (Wadke et al., 2016), exclusion of defenses by transport systems (Wang et al., 2013) and insensitivity to defenses by modifications of their cellular targets (Fry & Millar, 1972; Fry & Munch, 1975). Such traits can also circumvent the toxic effects of plant host volatiles allowing microbes to infect hosts that produce high levels of volatiles.

Cyanogenic glycosides are pre-formed plant defense metabolites that are hydrolyzed by specialized plant glucosidases upon tissue damage to form the volatile product hydrogen cyanide (HCN) gas. HCN is extremely toxic, as it inactivates cytochrome C, the terminal oxidase in the respiratory chain (Knowles & Bunch, 1986). Certain pathogens infecting the approximately 2000 plant species known to produce cyanogenic glycosides (Seigler, 1991) have adaptations allowing them to overcome the toxic effects of HCN. Among these, *Gloeocercospora sorghi*, a pathogen of sorghum, and *Stemphylium loti*, a pathogen of *Lotus corniculatus* (bird's-foot trefoil), have been studied most intensively (Fry & Munch, 1975; Fry & Millar, 1972). Both species possess cyanide hydratase, an enzyme that converts HCN into non-toxic formamide (Fry & Munch, 1975; Fry & Millar,

1972). This enzyme has also been found in other plant pathogens such as *Fusarium oxysporum* (Yanase, Sakamoto, Okamoto, Kita & Sato, 2000) and *F. solani* (Dumestre, Chone, Portal, Gerard & Berthelin, 1997). Through this pathway, some fungi can even utilize HCN as a nitrogen source (Dumestre et al., 1997); in others, formamide seems to be a dead-end product. However, it is not entirely clear if cyanide hydratase is a virulence factor for these pathogens, as it was shown that knocking out this enzyme in *G. sorghi* had no effect on the overall virulence of the fungus, but rendered it extremely sensitive to HCN *in vitro* (Wang, Sandrock, & VanEtten, 1999). This might be due to the presence of another trait that allows circumvention of hydrogen cyanide, such as a cyanide-insensitive respiration system mediated by an alternative oxidase in this fungus that can act as a terminal electron acceptor during respiration in a HCN-rich environment. In *S. loti*, for example, an alternative oxidase was expressed when the fungus was challenged with HCN *in vitro*, probably contributing to its success during infection of *L. corniculatus* (Rissler & Millar, 1977). *Microcyclus ulei*, a pathogen of the cyanogenic rubber tree, is thought to possess a similar mechanism to circumvent HCN toxicity, as it does not have a cyanide hydratase enzyme but thrives on hosts with higher levels of cyanogenic glycosides (Lieberei, 2012). In the rubber tree, higher levels of cyanogenic glycosides were less effective in controlling the fungus than other defenses, such as for example phenolic compounds (Lieberei, Biehl, Giesemann, & Junqueira, 1989). Therefore, the production of cyanogenic glycosides by plants does not always confer fitness benefits, especially during interactions with pathogens that have adapted to successfully circumvent this defense.

Another interesting example where a plant pathogen avoids the negative effects of host chemical defenses is in citrus, where high levels of the monoterpene (+)-limonene are accumulated in secretory cavities in the peel of mature fruit. Mature citrus fruit, however, are often infected by *Penicillium digitatum*. This pathogen is able to efficiently transform (+)-limonene to other terpenoids such as α-terpineol (Tan, Day & Cadwallader, 1998) and (+)-limonene might even be used by this fungus as a carbon source (Duetz, Bouwmeester, Van Beilen & Witholt, 2003). Thus (+)-limonene is no impediment to *P. digitatum* infection. Consistent with this, down-regulating the expression of the limonene synthase gene in orange fruit did not result in greater infection by *P. digitatum*, but instead fruit became more resistant to this fungus, as well as resistant to the bacterium *Xanthomonas citri* (Rodriguez et al., 2011[a,b]). Lower levels of limonene caused a higher expression of jasmonate signaling-related genes as well as genes of the phenylpropanoid pathway that might be involved in alternative forms of resistance to which *P. digitatum* is not adapted (Rodriguez et al., 2014). Since limonene production in citrus peels is at its highest when seeds have reached maturity, it has been proposed that limonene might even be an evolutionary mechanism by which the plant promotes microbial infection, softening the peel to release the seeds from the fruit for more

efficient seed dispersal (Rodriguez et al., 2011[b]; 2014). Although this hypothesis has not been tested, this could be an example where plant volatiles are used in a beneficial association with a microbial species.

The mountain pine beetle-associated fungus, *Grosmannia clavigera*, is an extremely interesting model for studying the adaptations of phytopathogenic fungi to host volatiles. This fungus infects pine trees that produce large amounts of terpenes stored in resin ducts. Upon beetle attack and infection by *G. clavigera,* the tree's resin ducts are damaged, releasing a toxic blend of volatile monoterpenes and sesquiterpenes, as well as non-volatile diterpene resin acids (Keeling & Bohlmann, 2006). As the fungus spends most of its life cycle in this terpene-rich environment, it is not surprising that *G. clavigera* has adapted to grow on monoterpene-rich substrates, using these volatiles as a carbon source (DiGuistini et al., 2011). Studies have shown that a large array of genes putatively involved in coping with terpenes are transcriptionally activated by additions of exogenous terpene mixtures to *in vitro* cultures of the fungus (DiGuistini et al., 2011; Wang et al., 2013; Wang et al., 2014). By making a knock-out mutant, Wang et al. (2013) showed that the fungus uses an ABC transporter to pump excess monoterpenes out of its cells. Inoculations of pine saplings with this mutant strain as well as *in vitro* feeding assays revealed that the efflux of monoterpenes is an important mechanism by which *G. clavigera* survives in its pine host. Furthermore, two gene clusters were identified in this fungus encoding enzymes involved in (+)-limonene degradation (Wang et al., 2014). Studies where individual genes involved in the degradation of this compound were knocked out revealed that (+) limonene is metabolized by initial oxidation and ring cleavage. The resulting carbon chains are then metabolized via β-oxidation (fatty acid metabolism) to form precursors of the valine catabolic pathway and the tricarboxylic acid cycle (Wang et al., 2014). Terpene oxidation and export from cells has also been observed in other conifer pathogens. For example, the weak sap-staining pine pathogen *Ophiostoma piceae* transcribes a similar ABC transporter as the one that was characterized in *G. clavigera* when cultured in a monoterpene mixture (Haridas et al., 2013). The cypress canker pathogen *Seiridum cardinale* detoxifies monoterpenes using similar oxidation reactions as those reported for *G. clavigera* (Achotegui-Castells et al., 2016).

Interestingly, genes involved in (+)-limonene degradation in *G. clavigera* were only transcribed 36 hours after co-cultivation with a terpene mixture as the sole carbon source (Wang et al., 2014), illustrating that in the case of this highly adapted fungus a long adjustment period is required to reprogram its metabolism for survival in the presence of terpenes. It is therefore not clear if such detoxification mechanisms also function in a timely manner in microbial pathogens that are exposed to plant volatiles during infection. However, microbes living in the phyllosphere have been suggested to employ volatiles as carbon sources that accumulate in the cuticle (reviewed by Farré-

Armengol, Filella, Llusia, & Peñuelas, 2016). A similar strategy might be utilized by plant pathogenic microbes that reside on the surface of host plants until conditions become favorable for infection. Host plant-derived volatiles might even be an important nutrient source for these organisms during the initial stages of infection (for example formation of infection cushions and infection pegs). However, the mechanisms by which phytopathogenic fungi can benefit from host plant volatiles during their free-living stage are yet to be elucidated.

4.2. Microbial manipulation of plant volatile profiles to attract insect vectors

Many plant pathogens, including a few fungi, some bacteria and most viruses, rely on insect vectors to disperse them (Table 2). Pathogens that require insects for their transmission usually have a close association with a single or a small group of related insect species (Eigenbrode, Bosque-Pérez, & Davis, 2018) and are acquired by their vector upon vector feeding. In many pathogen-vector associations, insects are rewarded by their pathogens with a fitness benefit, but in some cases, the insect is tricked by the pathogen and no fitness benefit is provided. To achieve high rates of dispersal, pathogens manipulate the behavior of insect vectors and this is often achieved through volatile cues (Eigenbrode et al., 2018).

Some fungal pathogens employ volatiles to mimic flowers and trick an insect into dispersing it. For example, McArt et al. (2016) showed that bees vector *Monilinia vaccinii-corymbosi,* the cause of mummy berry disease of blueberry, because infected leaves produce flower-like floral scent containing high levels of cinnamyl alcohol and cinnamyl aldehyde. Healthy leaves, on the other hand, do not produce these volatiles. Bees were shown to be attracted to diseased leaves, mistaking them for flowers, and thereby transmitting the disease during subsequent floral visits. Another example, where pathogens mimic floral volatiles is in the case of *Puccinia arrthenatheri*. This fungus produces pseudoflowers (Naef, Roy, Kaiser & Honegger, 2002; Raguso & Roy, 1998; Roy, 1993) which are rosettes of leaves encrusted with the brightly colored spermagonia of the rust that resemble true flowers. Interestingly, these pseudoflowers produce a floral fragrance and exude a fructose-rich solution that is consumed by foraging insects (Raguso & Roy, 1998). These floral mimics thus provide both visual and olfactory cues to attract bees and flies and even reward them with a sugary solution for dispersing their spores (Raguso & Roy, 1998).

Phytoplasmas are unculturable bacteria without cell walls that are limited to the phloem tissue of their host plants and depend on Hemipteran insect vectors, including leaf hoppers, plant hoppers and psyllids for their dispersal (Bertaccini & Duduk, 2009). Once they have been acquired by the insect, these bacteria move through the haemolymph to the salivary glands of the vector from

Table 2: Volatiles emitted by plants during pathogen infection that are attractive or repulsive to insect vectors

Host plant	Pathogen	Insect vector	Emitted volatile	Activity	Citation
	Fungi				
Ulmus americana	*Ophiostoma novo-ulmi*	*Hylurgopinus rufipes*	Mono- and sesquiterpenes	Attractive	McLeod et al., 2005
Vaccinium spp.	*Monilinia vaccinii-corymbosi*	*Apis mellifera*	cinnamyl alcohol, cinnamyl aldehyde	Attractive	McArt et al., 2016
Arabis spp.	*Puccinia monoica*	*Apis mellifera*	aromatic alcohols, aldehydes and esters	Attractive	Raguso & Roy, 1998
	Bacteria				
Malus domestica	*Erwinia amylovora*	*Apis mellifera*	Methyl salicylate	Repulsive	Cellini et al., 2019
Cucurbita pepo	*Erwinia tracheiphila*	*Acalymma vittatum*	(*E*)-2-hexenal	Attractive	Shapiro et al., 2012
Citrus sinensis	*Candidatus* Liberibacter asiaticus	*Diaphorina citri*	Methyl salicylate	Attractive	Mann et al., 2012
Malus domestica	*Candidatus* Phytoplasma mali	*Cacopsylla picta*	(*E*)-β-caryophyllene	Attractive	Mayer et al., 2008a; 2008b
Solanum lycopersicum	*Candidatus* Liberibacter solanacearum	*Bactericera* spp.	Increased levels of GLVs and terpenoids	Attractive-naïve vectors, Repulsive-infected vectors	Mas et al., 2014
	Viruses				
	Persistent, circulative				
Triticum aestivum	*barley yellow dwarf luteovirus*	*Rhopalosiphum padi*	Increased levels of GLVs and terpenoids	Attractive-naïve vectors, Repulsive-infected vectors	Jimenez-Martinez et al., 2004; Dos Santos et al., 2016
Solanum tuberosum	*potato leaf roll virus*	*Myzus persicae*	Increased levels of GLVs and terpenoids	Attractive-naïve vectors, Repulsive-infected vectors	Eigenbrode et al., 2002; Ngumbi et al., 2007; Rajabaskar et al., 2014; Werner et al., 2009
Nicotiana tabacum	*tomato yellow leaf curl virus*	*Bemisia tabaci*	Lower levels of terpenes	Attractive	Luan et al., 2013; Fang et al., 2013
Solanum lycopersicum	*tomato severe rugose virus*	*Bemisia tabaci*	Lower levels of terpenes	Attractive-naïve vectors, Repulsive-infected vectors	Fereres et al., 2016
	Non-persistent, non-circulative				
Cucurbita pepo	*cucumber mosaic virus*	*Aphis gossypii*	Increased emission of complex blend	Attractive	Mauck et al., 2010; Mauck et al., 2014
Solanum tuberosum	*potato virus X and Y*	*Myzus persicae*	Lower levels of GLVs and terpenes	No response	Eigenbrode et al., 2002
Cucurbita pepo	*zucchini yellow mosaic virus*	Generalist aphids	Lower levels of complex blend		Shapiro et al., 2012
Solanum lycopersicum	*tomato chlorosis virus*	*Bemisia tabaci*	Increased levels of terpenes	Repulsive	Fereres et al., 2016
Glycine max	*bean pod mottle virus*	*Epilachna varivestis*	Lower levels of complex blend	Repulsive	Penaflor et al., 2016
Glycine max	*soybean mosaic virus*	*Aphis glycines*	Lower levels of complex blend	Attractive	Penaflor et al., 2016

where they are transmitted to the host plant while the insect is feeding on the phloem. Phytoplasmas have been shown to alter the volatile profiles of hosts, such as citrus (Mann et al., 2012), pome fruit (Mayer, Vilcinskas, & Gross, 2008[a]; 2008[b]) and Solanaceae (Mas, Vereijssen, & Suckling, 2014) (Table 2). In all cases studied so far, the volatiles emitted from infected hosts were attractive to insect vectors. For example, citrus trees infected by *Candidatus* Liberibacter asiaticus (the first term indicates that this bacterium is unculturable) were more attractive to its psyllid vector (*Diaphorina citri*) due to higher emissions of methyl salicylate (Mann et al., 2012). Attraction was similar in phytoplasma-infected as well as naïve insect vectors that had not yet acquired the pathogen. Similarly, apple trees infected by *Candidatus* Phytoplasma mali emitted more *β*-caryophyllene than healthy trees and were more attractive to a psyllid (*Cacopsylla picta*) vector (Mayer et al., 2008[a]; 2008[b]). These bacteria are all acquired by insects during prolonged feeding periods on infected hosts (Bertaccini & Duduk, 2009). Enhanced attraction of vectors to infected hosts and their arrestment for long periods is therefore initially advantageous for the pathogen. However, efficient dispersal requires that vectors abandon infected hosts and subsequently feed on healthy plants. How this is achieved has rarely been studied. In one case, however, it was shown that phytoplasma-infected host plants may have lower nutrient levels (Mann et al., 2012) which in the long run could induce vectors to abandon them, thereby effectively dispersing the pathogen. Abandonment of infected hosts can also be induced by volatiles. For example, the volatile bouquet of tomato infected with *Candidatus* Liberibacter solanacearum was more attractive to naïve *Bactericera* spp. psyllid vectors, but was repulsive to vectors that had already acquired the bacterium (Mas et al., 2014). Attraction, arrestment and repulsion of insect vectors by plant volatiles in their interactions with healthy and infected plants are complex. Further studies are thus required to assess the importance of volatiles in these interactions.

Viruses are transmitted by aphids and other insects in the order Hemiptera, including white flies, thrips, plant- and leaf-hoppers (Eigenbrode et al., 2018). Viruses are vectored either by transient attachment to the stylet mouthparts of the insect (non-persistent, non-circulative viruses) or by migration in the vector haemolymph to the salivary glands from where they are transmitted during feeding (persistent, circulative viruses) (Eigenbrode et al., 2018). Persistent, circulative viruses are similar to phytoplasmas in that their vectors can only acquire them during prolonged feeding periods. Consequently, a number of studies have shown that circulative viruses attract their vectors to infected host plants via volatile cues (Table 2) and even reward vectors for feeding on the infected host by causing higher nutrient levels in the phloem (Eigenbrode, Ding, Shiel, & Berger, 2002; Fereres et al., 2016; Mauck et al., 2012; Vos & Jander, 2010). For example, wheat plants infected with the *barley yellow dwarf luteovirus* emitted higher levels of terpenes and GLVs and were more

attractive to aphids (*Rhopalosiphum padi*) than non-infected control plants (Jimenez-Martinez et al., 2004). Similar behavior was also recorded for *Myzus persicae* aphids on potato plants, which also produced higher levels of terpenoids and GLVs due to an infection by the *potato leaf roll virus* (Eigenbrode et al., 2002; Ngumbi, Eigenbrode, Bosque-Pérez, Ding & Rodriguez, 2007; Rajabaskar, Bosque-Pérez, & Eigenbrode, 2014). Interestingly, these studies demonstrated that only aphids which had not yet acquired the virus were attracted to the diseased plants, whereas aphids which had virus particles in their salivary glands were attracted to healthy control plants (Eigenbrode et al., 2002; Ingwell, Eigenbrode & Bosque-Pérez, 2012; Ngumbi et al., 2007; Rajabashkar et al., 2014;). Plants infected by the *potato leaf roll virus* were also more nutritious to aphids than uninfected control plants (Castle & Berger, 1993). However, in some cases, increased performance of the insect vector on a virus-infected host plant is the result of lower volatile emissions of the host (Table 2). For example, the *tomato yellow leaf curl China virus* as well as the *tomato severe rugose virus* suppressed volatile emissions that are normally induced in healthy hosts upon vector (*Bemisia tabaci*) feeding, thereby increasing the palatability of the plant for the white fly vector (Fang et al., 2013; Fereres et al., 2016; Luan et al., 2013).

Non-persistent, non-circulative viruses, on the other hand, benefit from short feeding intervals on infected hosts before the vector moves off to healthy plants (Mauck et al., 2012). Cucumber plants infected with *cucumber mosaic virus* emitted volatiles that were attractive to two aphid vectors, *M. persicae* and *Aphis gossypii*. However, the virus lowered the nutritional quality of its host plant to such an extent that the aphids rapidly abandoned the host after initial attraction in search of healthy hosts (Mauck, De Moraes & Mescher, 2010). On the other hand, lower volatile emissions were shown for host plants infected with non-circulative viruses such as *potato virus X and Y* (Eigenbrode et al., 2002). Similarly, cucurbit plants infected with *zucchini yellow mosaic virus* produced lower volatile emissions than healthy plants. Interestingly, in this system, lower volatiles emitted from virus infected flowers discourage the beetle vector of a bacterial disease, *Erwinia tracheiphila*, from visiting the flowers, and thus prevent secondary infections with this highly virulent competing pathogen (Shapiro, De Moraes, Stephenson & Mescher, 2012).

Although the information relayed by a single volatile cue can be highly specific, quantitative differences in mixtures are far more widely perceived by most insects. It is therefore not surprising that viruses depending on generalist insects such as the aphid species *R. padi* and *M. persicae* induce volatile emissions that increase quantitatively but not qualitatively (Ngumbi et al., 2007). On the other hand, phytoplasma species rely on specialist vectors and therefore produce a qualitatively different volatile bouquet in their hosts to attract specific vector species (Table 2).

Volatiles emitted during insect herbivore feeding are often used by parasitoids and predators of herbivores to locate their prey (Turlings & Erb, 2018). Enhanced volatile emission by infected plants might thus be used by natural enemies of insect vector species for locating their prey or parasitic hosts. For example, Martini, Pelz-Stelinski, & Stelinski (2014) showed that increased methyl salicylate produced by plants infected by *C.* Liberibacter asiaticus attracted not only the vector *D. citri*, but also natural enemies of *D. citri*, which constituted a dramatic fitness cost for this insect. Methyl salicylate also attracts ladybird beetles (*Coccinella septempunctata*), which are voracious predators of Hemipteran insects (Zhu & Park, 2005). On the other hand, the thrips, *Frankliniella occidentalis,* benefitted from feeding on plants infected by *tomato spotted wilt virus* by developing faster than on control plants and thus escaped from predatory mites (Belliure, Janssen & Sabelis, 2008). The role of plant volatiles is thus often highly context-dependent in natural microbe-insect vector associations, and the cost-benefit balance of volatile production might differ depending on the species involved and the surrounding ecosystem.

5. Conclusions and outlook

Plant volatiles have long been known for their anti-microbial activity. Yet much more research has been carried out on the roles of volatiles in defense against herbivores than defenses against microbes. However, research on volatile-pathogen interactions is increasing with attention being paid not only to the direct toxicity and deterrency of volatiles, but also to the importance of induced volatiles in activating other plant defense responses. Individual volatiles might even have both roles although many more experiments are needed with volatiles being supplied by plants at naturally emitted rates rather than directly applied at unrealistically high doses, as is common practice.

The lack of research on volatile-pathogen interactions may result from the fact that many plant pathogens appear to be unaffected by volatiles due to their ability to detoxify them or circumvent their effects in other ways. Yet the ability of pathogens to exploit plant volatiles as nutrient sources or attractants for insect vectors indicates a rich variety of plant-microbe interactions that may be mediated by volatiles. Studies investigating volatiles as defenses against herbivores have created numerous analytical and molecular tools, including sensitive protocols for quantifying volatile emission (Tholl et al., 2006) and transgenic plants impaired in their ability to produce or perceive volatiles (Baldwin, Halitschke, Paschold, van Dahl & Preston, 2006). These and other tools can now be utilized for studying the different roles of volatiles in plant-pathogen interactions. More knowledge on volatile plant defenses against pathogens may provide new

sustainable disease management options for agriculture and forestry applications and should facilitate the discovery of novel direct as well as indirect defense mechanisms against economically important plant diseases.

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Author contributions:

The authors contributed equally

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