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Bacterial Volatile Compounds: Functions in Communication, Cooperation, and Competition

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Abstract

Bacteria produce a multitude of volatile compounds. While the biological functions of these deceptively simple molecules are unknown in many cases, for compounds that have been characterized, it is clear that they serve impressively diverse purposes. Here, we highlight recent studies that are uncovering the volatile repertoire of bacteria, and the functional relevance and impact of these molecules. We present work showing the ability of volatile compounds to modulate nutrient availability in the environment; alter the growth, development, and motility of bacteria and fungi; influence protist and arthropod behavior; and impact plant and animal health. We further discuss the benefits associated with using volatile compounds for communication and competition, alongside the challenges of studying these molecules and their functional roles. Finally, we address the opportunities these compounds present from commercial, clinical, and agricultural perspectives.

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1. INTRODUCTION TO BACTERIAL VOLATILE COMPOUNDS

Bacteria are ubiquitous, and their survival in diverse niches requires the ability to effectively coexist and compete with organisms from all domains of life. Bacteria can influence the dynamics and composition of their local communities through the production of secondary metabolites like antibiotics and toxins. These microbes are, however, also prolific producers of volatile organic compounds, and over the last ~10 years, our appreciation for the biological roles played by these volatile compounds has grown. Bacterial volatiles are now recognized for their function as potent antimicrobial weapons, long-range communication signals, behavioral modulators, and important mediators of commensal relationships.

Volatile compounds are small, low-molecular-weight (<300 Da), often odorous molecules whose high vapor pressure and low boiling points mean they disperse easily through air and water (7, 78, 80). To date, thousands of microbial volatiles belonging to different chemical classes have been identified, with the majority of these comprising alcohols, aromatic compounds, ketones, terpenes, organic acids, esters, aldehydes, sulfur compounds, alkanes, and alkenes (22, 46, 50, 76) (**Table 1**); it is likely that many more remain to be discovered. Bacteria emit a larger and more diverse set of volatile compounds than fungi (76). Their repertoire of volatile compounds can be highly variable, even within species, and volatile production is influenced by a multitude of factors (42, 57).

Bacterial volatile compounds can elicit physiological responses in other bacteria and fungi and can impact the growth and health of higher-order organisms like plants (45, 64) and animals (75, 104). To date, they are best understood in the context of microbial soil communities (24, 40, 63, 100), although this is starting to change. Recent reviews have focused on the effects of volatiles on bacterial biology, and their contributions to intra- and interkingdom interactions (1, 3, 77, 80, 82). Here, we focus on summarizing recent literature, particularly on bacterial volatiles and their impacts on the growth and behavior of organisms from multiple domains of life. This review further addresses the benefits and shortcomings of volatiles as a means of communicating and competing and discusses the opportunities and open questions in the field.

Table 1 Examples of bacterial volatile compounds with functional assignments

Compound	Chemical Class	Known Effect(s)	Producing Organism(s)	References
1-Dodecanol	Alcohol	Found in preen oil	Various	102
1-Octen-3-ol	Alcohol	Antifungal activity	*Paenibacillus* sp.	37
1-Tridecanol	Alcohol	Found in preen oil	Various	102
2-Phenylethanol	Alcohol	Antifungal activity	*Paenibacillus polymyxa*	73
3-Methylbutanol	Alcohol	Antifungal activity	*Bacillus pumilus* TM-R	60
Caryolan-1-ol	Alcohol	Antifungal activity	*Streptomyces* sp.	15
Ethanol	Alcohol	Antifungal activity	*Bacillus pumilus* TM-R	60
Isobutanol	Alcohol	Antifungal activity	*Paenibacillus polymyxa*	73
Phenylethyl alcohol	Alcohol	Antifungal activity	*Streptomyces* sp.	103
Acetaldehyde	Aldehyde	Antibacterial activity	*Escherichia coli*	51
Decanal,3,5-dimethylbenzaldehyde	Aldehyde	Protist attractant	*Listeria monocytogenes*	29
Glyoxylic acid	Aldehyde	Alters bacterial gene expression	*Bacillus subtilis*	47
1-Undecene	Alkene	Antifungal activity	*Pseudomonas* sp.	39, 52
Formamide	Amide	Enhances plant growth	*Pseudomonas fluorescens*	106
N,N-dimethylformamide	Amide	Enhances plant growth	*Pseudomonas fluorescens*	106
Ammonia	Amine	Raises pH, alters antibiotic resistance profiles	Various	2, 42–44, 61
Putrescine	Amine	Alters antibiotic resistance profile	*Burkholderia cenocepacia*	25
S-(−)-2-methylbutylamine	Amine	Antifungal activity	*Bacillus pumilus* TM-R	60
Trimethylamine	Amine	Raises pH, antibacterial activity, communication molecule	*Streptomyces venezuelae*, *Escherichia coli*	42–44, 50
2,5-Bis(1-methylethyl)-pyrazine	Aromatic compound	Antibacterial activity	*Paenibacillus* spp.	41, 94
2,5-Dimethyl pyrazine	Aromatic compound	Antifungal activity	*Bacillus pumilus*	37
2,6-Bis-(2-methylpropyl) pyrazine	Aromatic compound	Antifungal activity	*Paenibacillus* sp.	37
Benzaldehyde	Aromatic compound	Antifungal activity, enhanced plant growth	*Pseudomonas* sp.	20, 106
Indole	Aromatic compound	Bacterial growth promoter, alters antibiotic resistance profiles, alters bacterial gene expression	Various	21, 49, 58
2,3-Butanedione	Diketone	Alters bacterial gene expression	*Bacillus subtilis*	47
Acetate	Ester	Alters bacterial gene expression	Various	14
Butyl 2-methylbutanoate	Ester	Influences mosquito behavior	Various	98
Butyl acetate	Ester	Influences mosquito behavior	Various	98
Butyl butyrate	Ester	Influences mosquito behavior	Various	98

(*Continued*)

Table 1 (*Continued*)

Compound	Chemical Class	Known Effect(s)	Producing Organism(s)	References
Ethyl acetate	Ester	Protist attractant	*Listeria monocytogenes*	29
Ethyl-isovalerate	Ester	Enhances plant growth	*Pseudomonas* sp.	11
Methyl isovalerate	Ester	Reduces fungal toxin production	*Alcaligenes faecalis*	31
3-Methyl butanoic acid	Fatty acid	Influences mosquito behavior	Various	98
2,3-Butanediol	Glycol	Enhances plant growth, reduces plant susceptibility to infection, antibacterial activity, alters bacterial gene expression	Various	18, 51, 61
1,3,5-Trichloro-2-methoxy benzene	Ketone	Antifungal activity	*Streptomyces* sp.	16
1-Methylthio-3-pentanone	Ketone	Alters antibiotic resistance profile	*Burkholderia ambifaria*	32
2′-Aminoacetophenone	Ketone	Induces persister cell formation	*Pseudomonas* sp., *Burkholderia* sp., *Acinetobacter* sp.	67
2-Heptanone	Ketone	Antibacterial activity	*Pseudomonas* sp.	66
2-Nonanone	Ketone	Antibacterial activity	*Pseudomonas* sp.	66
2-Pentadecanone	Ketone	Found in preen oil	Various	102
2-Tetradecanone	Ketone	Found in preen oil	Various	102
2-Tridecanone	Ketone	Found in preen oil	Various	102
2-Undecanone	Ketone	Antibacterial activity	*Pseudomonas* sp.	66
4-Hydroxy-2-pentanone	Ketone	Antifungal activity	*Pseudomonas* sp.	20
5-Methyl-2-heptanone	Ketone	Antifungal activity	*Bacillus pumilus* TM-R	60
Acetoin	Ketone	Enhances plant growth, promotes root growth, increases number of lateral roots	Various	28, 72
Butan-2-one	Ketone	Antifungal activity	*Streptomyces griseus*	38
Methyl isobutyl ketone	Ketone	Antifungal activity	*Pseudomonas aeruginosa*	60
O-aminoacetophenone	Ketone	Alters antibiotic resistance profile	*Escherichia coli*	32
Schleiferon A	Ketone	Antibacterial activity	*Staphylococcus schleiferi*	50
Schleiferon B	Ketone	Antibacterial activity	*Staphylococcus schleiferi*	50
(E)-12-methyltridec-3-enenitrile	Nitrile	Antifungal activity	*Pseudomonas* sp., *Micromonospora* sp.	59
3-Pentadecenenitrile	Nitrile	Antibacterial activity	*Pseudomonas* sp., *Micromonospora* sp.	59
Nitric oxide	Nitrogenous compound	Alters antibiotic resistance profiles	*Bacillus subtilis*	33, 34
Dimethyl disulfide	Sulfur compound	Antifungal activity, influences mosquito behavior, enhances plant growth, reduces fungal toxin production	*Pseudomonas* sp., *Microbacterium* sp., *Serratia* sp., *Bacillus pumilus*, *Alcaligenes faecalis*	17, 52, 60, 66, 93, 98

(*Continued*)

Table 1 (*Continued*)

Compound	Chemical Class	Known Effect(s)	Producing Organism(s)	References
Dimethyl sulfide	Sulfur compound	Bacterial growth promoter	*Pseudomonas aeruginosa*	9, 84
Dimethyl trisulfide	Sulfur compound	Enhances plant growth	*Microbacterium* sp.	17
Hydrogen sulfide	Sulfur compound	Alters antibiotic resistance profiles	*Bacillus subtilis*	33, 34
Methanethiol	Sulfur compound	Antifungal activity	*Pseudomonas tolaasii*	52
2-Methylisoborneol	Terpene	Springtail attractant	*Streptomyces* sp.	4
Geosmin	Terpene	Springtail attractant; *Drosophila* repellant	*Streptomyces* sp.	4

2. IMPACT OF BACTERIAL VOLATILES ON PRODUCERS AND NEIGHBORING BACTERIA

Classical laboratory studies of bacterial monocultures in rich medium have yielded a wealth of information about bacterial biology, but they have failed to capture the complex, dynamic interactions that occur between organisms. As more research turns toward multispecies coculture, volatile compounds are featuring more prominently, given their readily diffusible properties and their ability to influence inter- and intraspecific bacterial interactions and behaviors. Indeed, volatile molecules are now known to serve as competitive weapons (e.g., volatile antibiotics), public infochemicals that can modulate gene expression and local behavior, environmental modulators that can alter the nutrient landscape, and protective compounds that can enhance cellular defense.

2.1. Volatiles That Antagonize Bacterial Growth and Change the Environment

A multitude of bacterial volatile molecules have been identified that can antagonize the growth of neighboring organisms (**Figure 1**). In a broad test for phenotypic impact, a panel of 14 volatile compounds produced by *Escherichia coli* were administered as pure solutions in compartments that shared airspace with cultures of *Pseudomonas aeruginosa*, *Bacillus subtilis*, *Staphylococcus aureus*, or *E. coli* (51). Acetaldehyde and 2,3-butanediol were toxic to all organisms at the tested concentrations, although whether these were at physiologically relevant levels is unclear. Bacterial growth was also indirectly affected by ammonia and trimethylamine (TMA), which sensitized bacteria to a range of antibiotics, including chloramphenicol and the aminoglycosides. TMA exposure also led to increased sensitivity to oxidative damage (51).

E. coli is not unique in producing these compounds, with *Streptomyces* species also being capable of emitting both TMA and ammonia (alongside many other volatile compounds) under specific growth conditions (42, 43). Recent work has revealed that TMA can function both as a communication tool and as a competitive weapon for *Streptomyces venezuelae*. When challenged with fungal competitors or when grown in a glucose-depleted environment, *S. venezuelae* switches from its classical sporulating life cycle to a growth mode termed exploration, in which nonbranching mycelial cells expand rapidly outward. During exploration, *S. venezuelae* produces large amounts of TMA, and this leads to a rise in the pH of the surrounding environment. This volatile-mediated environmental alkalinization serves as a positive, feed-forward signal, inducing the switch from classical development to exploration in physically separated *Streptomyces*. The TMA-driven rise in pH also serves to alter nutrient levels in the environment, specifically reducing the bioavailability of iron, an essential micronutrient. This resulting iron scarcity severely limits the growth of other nearby microbes, including the bacteria *B. subtilis* and *Micrococcus luteus* and the fungus *Saccharomyces cerevisiae*; growth of these microbes could be rescued by supplementation with

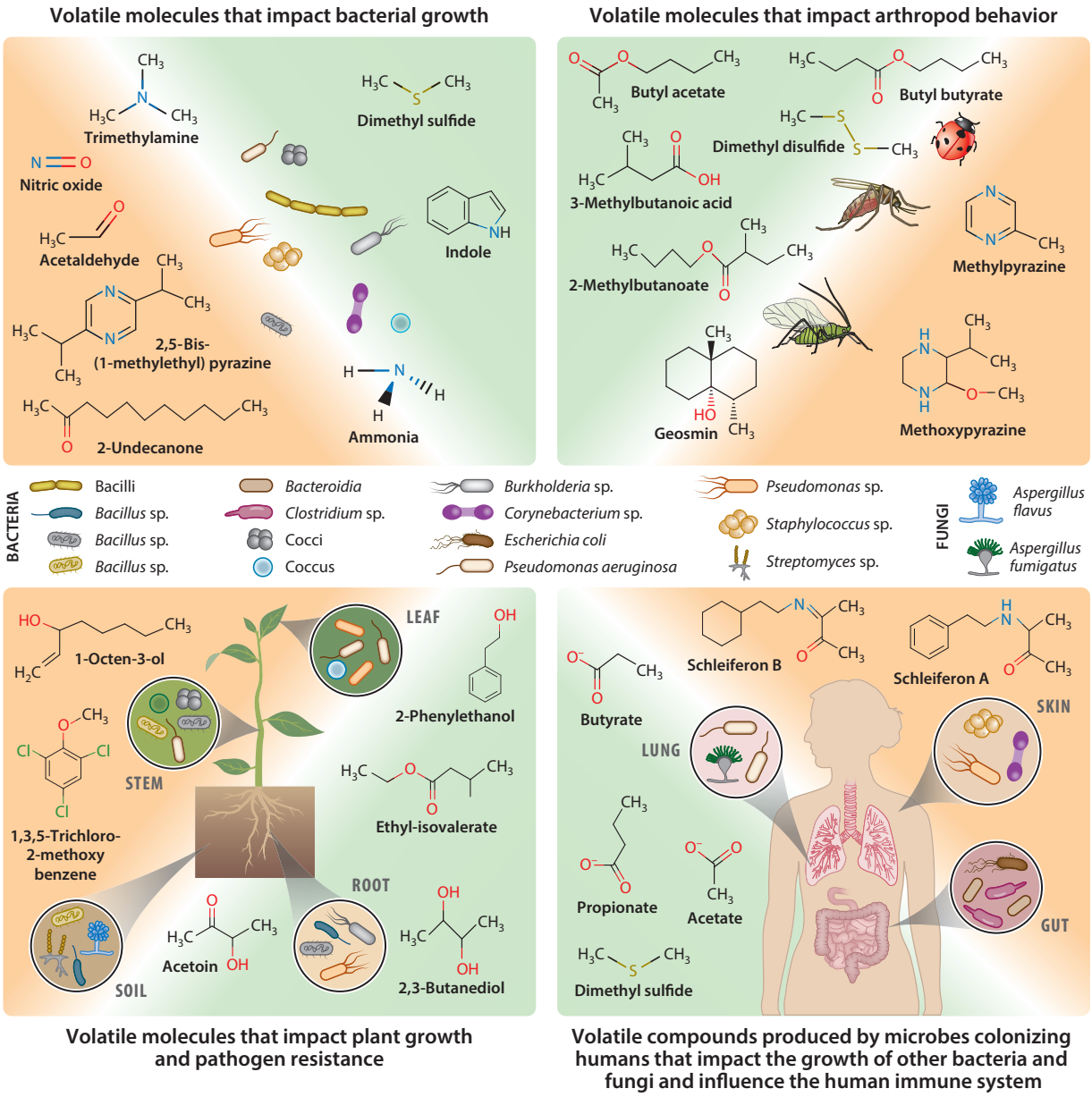

Figure 1

Bacterial volatiles can exert positive (*green*) and negative (*orange*) effects on the growth and behavior of a wide range of organisms. Molecules shown at the green-orange interface are ones that can have either positive or negative effects. Figure adapted from image created with BioRender.com and MarvinSketch.

additional iron (44). Whether such volatile-mediated nutrient modulation is a common phenomenon in soil environments remains to be seen.

Subsequent studies of *Streptomyces* volatile-mediated antagonism have revealed that a number of *Streptomyces* species, including *S. venezuelae*, *S. griseus*, *S. coelicolor*, and *Streptomyces* sp. MBT11,

can produce biogenic ammonia during classical (nonexploratory) growth (2). As with TMA, ammonia accumulation can alkalinize the medium, and at sufficient levels, this results in reduced growth of physically separated *E. coli*. Ammonia (and TMA) is known to sensitize *E. coli* and *B. subtilis* to an array of antibiotics (2, 6, 51), and as *Streptomyces* species are renowned producers of antibiotics, these volatiles may represent previously unappreciated adjuvants of antibiotic activity.

While the amino group–containing ammonia and TMA are well-established bioactive bacterial volatiles, biogenic nitriles can also function in volatile forms. Volatile profiling of *Pseudomonas veronii* and *Micromonospora echinospora* revealed that these phylogenetically divergent species both emit fatty acid–derived long-chain alkyl nitriles (59). Several of these had biological effects: 3-Pentadecenenitrile inhibited the growth of various gram-positive bacteria, including *B. subtilis*, *M. luteus*, and *S. aureus*, while (E)-12-methyltridec-3-enenitrile had antifungal activity (59).

Increasingly, the volatile compounds produced by soil-dwelling bacteria are being found to modulate—and be affected by—microbial community interactions and community composition. Coculturing of *Paenibacillus* sp. and *Burkholderia* sp. on solid medium led to reduced *Burkholderia* growth and production of 19 volatile compounds that were not detected in their respective monocultures (94). Gas chromatography–mass spectrometry (GC-MS) identified 2,5-bis(1-methylethyl)-pyrazine as an abundant volatile produced by *Paenibacillus* during this coculture, and the pure synthetic compound could recapitulate the growth-inhibitory effects on *Burkholderia* (41). The volatile capacity of the biocontrol bacteria *Pseudomonas fluorescens* and *Bacillus amyloliquefaciens* has also been assessed, in association with their effects on the bacterial plant pathogen *Ralstonia solanacearum* (69, 70). Analysis of the complex volatile mixture produced by each species revealed that 10 of the 13 molecules identified for *P. fluorescens* and 13 of the 25 for *B. amyloliquefaciens* inhibited the growth and root colonization of *R. solanacearum*, suggesting that the volatile repertoire of these biocontrol microbes may function to protect plants from bacterial pathogens. Analogous observations were made for the rhizospheric bacteria *Pseudomonas chlororaphis*, *Serratia proteamaculans*, and *Serratia plymuthica*, all of which displayed volatile-mediated inhibition of the plant pathogen *Agrobacterium tumefaciens* (66). Solid-phase microextraction (SPME) followed by GC-MS revealed that the *Pseudomonas* species produced 2-nonanone, 2-heptanone, and 2-undecanone as minor volatile components, while the *Serratia* species produced dimethyl disulfide as their main volatile component. These four compounds killed *A. tumefaciens* in mature biofilms and inhibited the formation of new biofilms when applied as pure, commercially available forms (66).

Volatile compounds and their producing bacteria have been best studied in the context of soil environments; however, two dominant families of the skin microbiome, *Staphylococcaceae* and *Corynebacteriaceae*, are also prolific volatile producers (50). Over 50 unique volatile compounds were identified from the screen of *Staphylococcaceae*, with >30 being reported for isolates of *Staphylococcus schleiferi* alone. During characterization of the volatiles produced by *S. schleiferi*, the ketones schleiferon A and B were discovered. These molecules inhibited the growth of other gram-positive skin bacteria and, interestingly, blocked quorum-sensing-regulated pathways in select gram-negative species (50).

2.2. Volatiles That Promote Bacterial Growth

While volatile compounds can be used for long-range competition by bacteria to inhibit the growth of their neighbors, volatiles can also protect and enhance the growth of both their producers and bacteria in the surrounding vicinity (**Figure 1**). As discussed above, TMA and ammonia released by *E. coli* and *Streptomyces* species can inhibit the growth of nearby bacteria and potentiate antibiotic-mediated growth inhibition (2). However, TMA can also promote and enhance the rapid expansion of *Streptomyces* colonies through exploratory growth (43). Ammonia,

paradoxically, can also indirectly benefit its producers and neighboring bacteria by enhancing resistance to specific antibiotics. For example, ammonia release promotes increased antibiotic resistance in physically separated *Serratia* colonies through a pH-dependent mechanism (12). Volatile ammonia produced by *E. coli* can also confer resistance to tetracycline in physically separated cultures of *P. aeruginosa*, *B. subtilis*, *S. aureus*, and *E. coli* (6). Mechanistically, this appears to be due to increased polyamine synthesis in response to ammonia uptake. Higher intracellular polyamine concentrations led to changes in membrane permeability that altered antibiotic resistance and susceptibility to oxidative stress (6). A volatile polyamine-mediated defense system has also been observed in *Burkholderia cenocepacia* (25). Exposure to the cationic antimicrobial peptide polymyxin B leads to the overproduction and secretion of the volatile polyamine putrescine by *B. cenocepacia* cells. This cationic amine binds the negatively charged gram-negative cell membrane where it is thought to outcompete polymyxin B, thereby enhancing resistance to this peptide antibiotic. Notably, this volatile small molecule can be sensed by physically separated cells, leading to increased resistance to polymyxin B in nearby community members (25). Volatile-mediated antibiotic resistance appears to be relatively common among the *Burkholderia* species, with a variety of volatile compounds produced by *Burkholderia ambifaria* (including 1-methylthio-3-pentanone and *O*-aminoacetophenone) promoting increased gentamicin and kanamycin resistance in physically separated *E. coli* cultures (32), although the underlying mechanism remains to be determined in this instance.

As the above examples indicate, the benefits associated with volatile production are not confined to the producer organisms, and a frequent outcome is altered antibiotic susceptibility, albeit through a variety of different means. In the case of indole, this abundant volatile compound is produced by a wide range of bacterial species (49), and included among its effects are an indirect positive influence on the growth of *Pseudomonas putida* (58). Upon sensing indole in the environment, *P. putida* upregulates the expression of an efflux pump that confers resistance to the antibiotic ampicillin. Another *Pseudomonas* species, *P. aeruginosa*, can also make use of small volatile molecules to reduce antibiotic susceptibility at a distance (67). Increased concentrations of 2′-aminoacetophenone signal *P. aeruginosa* to markedly decrease translation in the cell. This leads to subpopulations of metabolically inactive persister cells that are tolerant to multiple classes of antibiotics. In addition to acting as an intraspecific signal for persister cell formation, 2′-aminoacetophenone could also promote persistence in the unrelated *Burkholderia thailandensis* and *Acinetobacter baumannii* (67).

Volatiles can improve bacterial growth and survival indirectly by reducing susceptibility to antibiotics; however, there is increasing evidence—often from mixed coculture experiments—that volatile compounds can also directly stimulate the growth of separated bacteria. In a two-compartment culture system, two methanotrophs, *Methylobacter luteus* and *Methylocystis parvus*, were grown adjacent to, but not contacting, *Bacillus pumilus*, *Bacillus simplex*, *Exiguobacterium undae*, *Pseudomonas mandelii*, and *Stenotrophomonas maltophilia* (97). Growing different combinations of methanotrophs and heterotrophs in adjacent compartments stimulated methane oxidation and enhanced the growth of physically separated methanotrophs, compared with monoculture controls. Volatile profiling by GC-MS revealed the volatile compounds produced during coculture were distinct from any monoculture, although the specific molecules responsible for the observed growth promotion have yet to be identified. Volatile profiles also differed for mixed culture versus monoculture communities of *Burkholderia*, *Dyella*, *Janthinobacterium*, *Pseudomonas*, and *Paenibacillus* species, grown in sandy soil enriched with an artificial root exudate (83). Intriguingly, the volatiles produced by the mixed cultures grown with root exudate supplementation could stimulate the growth of physically separated bacteria grown in nutrient-poor

soil, perhaps serving as a chemoattractant, signaling the presence of a nearby nutrient-rich environment (83).

The effects of volatile compounds can also be complex and multifaceted, as demonstrated by a study looking at the volatile profiles, and the effects of these compounds in monoculture and pairwise combinations of *Chryseobacterium*, *Tsukamurella*, *Dyella*, and *Janthinobacterium* species. Volatile abundances changed between monocultures and cocultures (95), and diverse effects were observed for these, with all volatile combinations adversely impacting fungal growth, the *Dyella* monoculture stimulating the growth of *S. aureus*, and the *Dyella-Janthinobacterium* coculture inducing morphological changes in *Serratia marcescens* without affecting viability.

Outside of low-molecular-weight organic products, small inorganic gases have also been shown to mediate protective effects in bacteria. Nitric oxide (NO), synthesized by *B. subtilis* and a small subset of other bacteria, can protect its producer from a diverse array of antibiotics by directly reacting with the inhibitory molecule, rendering it inactive (34). NO can also enhance the oxidative stress response in *B. subtilis*, by both potentiating catalase activity, where catalase functions to detoxify hydrogen peroxide, and decreasing the presence of free sulfhydryl groups, which can participate in Fenton reactions and generate reactive oxygen species (33). Additionally, hydrogen sulfide (H_2S), often considered a volatile by-product of many bacterial species, can synergize with NO and contribute to cellular defenses (85). In *Bacillus anthracis*, *E. coli*, *S. aureus*, and *P. aeruginosa*, H_2S production bolstered antibiotic resistance, again by increasing the cellular capacity to respond to oxidative stress through stimulating superoxide dismutase and catalase activity and sequestering Fe^{2+} ions to minimize the production of reactive oxygen species (85).

2.3. Volatiles That Alter Bacterial Gene Expression and Bacterial Behavior

Many of the volatile compounds that stimulate or suppress bacterial growth in one system can promote interesting genetic and behavioral changes in another. A community-based study sampled the transcriptome of *P. fluorescens* under rich soil conditions, when it was grown in association with volatiles produced from monocultures of *Collimonas pratensis*, *S. plymuthica*, *Paenibacillus* sp., *Pedobacter* sp., and a mixture of the four species (30). Each condition yielded a different blend of volatiles and promoted differential expression of varying numbers of *P. fluorescens* genes (ranging from 83 to 325 genes), of which only a subset (22 genes) were common to all cocultures, providing a powerful illustration of how distinct volatile species and combinations can elicit unique genetic and chemical responses in other organisms. An independent investigation focused specifically on the interaction/response of *E. coli* to volatile compounds produced by *B. subtilis* when grown in close proximity. Transcriptomic analyses revealed that genes related to motility and toxin-antitoxin systems were upregulated, and subsequent investigations revealed a change in *E. coli* swarming motility (47). This behavioral response by *E. coli* was confirmed using the commercially available volatile solutions 2,3-butanedione and glyoxylic acid, to which exposure led to a similar reduction in swarming motility (47).

This change in bacterial motility in response to volatile compounds is not unique to *E. coli* and *Bacillus* species. Indeed, the nonmotile *Paenibacillus vortex* produces a volatile compound capable of stimulating *Xanthomonas perforans* motility, directing it toward the *P. vortex* colony (36). When the two organisms were cocultured without barriers on plant material, it was discovered that the volatile compounds emitted by *P. vortex* functioned as a chemoattractant for *X. perforans*, with the resulting motile raft of *X. perforans* cells being used to disperse *P. vortex* to new locations along the plant surface (36).

In addition to impacting motility, an assortment of bacterial volatiles can trigger changes in biofilm development. Extracellular concentrations of the volatile molecule indole can be sensed

by *E. coli* to induce biofilm formation (21), while *B. subtilis* can promote biofilm formation in nearby (but physically separated) colonies through the production of the volatile compound acetate (14). Acetate, along with other common volatile fermentation products including lactate, ethanol, and 2,3-butanediol, has also been tested for its impact on *P. aeruginosa* in the context of cystic fibrosis infections (96). Exposure of *P. aeruginosa* to 2,3-butanediol (but not acetate) stimulated biofilm formation, decreased swimming and swarming motility, and led to the production of compounds active against *S. aureus* and *S. marcescens*. Ammonia, which as discussed above can inhibit bacterial growth and modulate antibiotic susceptibility, can also promote biofilm formation. In multiwell culture experiments involving *Bacillus licheniformis*, ammonia produced by cultures in neighboring wells stimulated both biofilm formation and pigmentation, with the strength of induction being inversely proportional to the distance between wells (61).

3. INTERKINGDOM INTERACTIONS MEDIATED BY BACTERIAL VOLATILES

While bacterial volatiles can profoundly impact—both positively and negatively—the growth and behavior of other bacteria, their effects extend well beyond the bacterial realm. The following section covers the role of volatile compounds in the interplay between bacteria and other organisms, ranging from lower eukaryotes to higher vertebrates.

3.1. Volatiles That Modulate Bacterial-Fungal Interactions

It is well established that bacterial volatiles can affect fungal development, particularly that of plant pathogens. In the 1960s, volatile compounds produced by *Streptomyces griseus* were found to trigger sclerotium (dormant structure) formation by the plant-pathogenic fungi *Sclerotium cepivorum* and *Rhizoctonia solani* and to reduce sporulation by *Gloeosporium aridum* (54). Investigations in the 1980s continued to uncover roles for *Streptomyces* volatiles on fungal behavior, with butan-2-one produced by *Streptomyces griseoruber* being capable of inhibiting spore germination of the pathogen *Cladosporium cladosporioides* (38). Streptomycetes are, however, not the only producers of volatiles that can impact fungal cells. *B. subtilis* also produces volatile compounds with antifungal capabilities, inhibiting the growth of *R. solani* and *Pythium ultimum* (27). Indeed, many bacteria appear capable of producing fungus-affecting volatile compounds. In 2007, more than 1,000 soil bacteria were surveyed for their ability to produce fungistatic volatile compounds. Nearly one-third (328) of these bacteria produced volatiles that inhibited spore germination and mycelial growth of the nematicidal fungi *Paecilomyces lilacinus* and *Pochonia chlamydosporia* (107). Phylogenetic analyses revealed five main groups of volatile producers: *Rhizobiaceae*, *Xanthomonadaceae*, *Micrococcaceae*, *Alcaligenaceae*, and *Bacillales*, of which members of the order *Bacillales* were most abundant. Efforts to identify the fungistatic volatile compounds involved using SPME-GC-MS. A number of bacterial volatile compounds were identified, with benzaldehyde, phenylacetaldehyde, and benzothiazole having known fungistatic properties (107).

Many of the best-characterized interactions between bacteria and fungi involve soil isolates. This holds true for investigations into volatile activities, where bacteria are the primary, but not exclusive, producers, and where reciprocal effects can be seen. A two-way volatile interaction has been described for the plant-pathogenic bacterium *R. solanacearum* and the plant-pathogenic fungus *Aspergillus flavus* (88). Volatiles produced by *R. solanacearum* resulted in both decreased conidiation by *A. flavus* and increased aflatoxin production by the fungus. Conversely, exposure of *R. solanacearum* to fungal volatiles led to a decreased growth rate, reduced melanin production, and increased extracellular polysaccharide production (88). SPME-GC-MS analyses revealed that

multiple volatiles were produced only by cocultures of these two organisms (88), although whether the responses detailed above were the result of one or more of these compounds remains to be determined. Reciprocal volatile effects were also seen for the biocontrol bacterium *Paenibacillus polymyxa* and the pathogenic fungus *Verticillium longisporum* (73). *P. polymyxa* emits volatiles that inhibit the growth of the wilt-causing fungus *V. longisporum* and lead to the simultaneous downregulation of fungal metabolic activities and activation of antimicrobial compound production (e.g., isobutanol, 2-phenylethanol) (73). At the same time, exposure of *P. polymyxa* to fungal volatiles results in a general upregulation of metabolic activity in the bacterium (73).

Interactions between soil-dwelling bacteria and fungi have been extensively studied; however, interactions between these groups also have important implications for human health. The fungus *Aspergillus fumigatus* and the bacterium *P. aeruginosa* frequently coinhabit the lungs of cystic fibrosis patients, where they compete for nutrients. Surprisingly, dimethyl sulfide produced by *P. aeruginosa* promotes the growth of *A. fumigatus* when they are physically separated, but not when they are competing for the same physical space (9, 84) (**Figure 1**). These sulfur-containing volatiles appear to be assimilated using the fungal cysteine (CysB) and homocysteine (CysD) synthases, and in doing so, they confer a growth benefit to *A. fumigatus*. *P. aeruginosa* produces dimethyl sulfide in *Galleria mellonella* (greater wax moth) larval infection models, and coinfection of *P. aeruginosa* with wild-type *A. fumigatus* results in significantly increased larval mortality, compared with coinfection with a *cysB/cysD A. fumigatus* mutant (84). These findings suggest that coinfection with both pathogens can result in more adverse infection outcomes (9).

Given that bacterial volatiles can impact—and often inhibit—the growth of pathogenic fungi, there is considerable interest in working to exploit these volatile compounds for commercial benefit. In an attempt to identify promising antifungal volatile compounds, a broad screen of 136 bacterial isolates was undertaken (60). From this screen, *Bacillus pumilus* TM-R showed the strongest and broadest antifungal volatile activity, suppressing growth of the pathogenic *Alternaria alternata*, *Cladosporium cladosporioides*, *Curvularia lunata*, *Fusarium oxysporum*, and *Penicillium italicum* fungi. In investigating the volatile compounds responsible for fungal mycelial growth inhibition, Morita et al. (60) identified 22 volatile compounds. Of these, 3-methylbutanol and dimethyl disulfide were known to have antifungal activity, although interestingly, they did not have the greatest antifungal effects. This honor belonged to 4 other volatile molecules: methyl isobutyl ketone, 5-methyl-2-heptanone, S-(−)-2-methylbutylamine, and ethanol. Notably, the first 3 compounds have not been previously reported to have antifungal properties, and thus they may be new candidates for use in, e.g., preventing fungal spoilage of food supplies (60).

Beyond simply inhibiting fungal growth, bacterial volatiles can also be used to reduce fungal toxin production. Aflatoxin, produced by *A. flavus*, is among the most dangerous mycotoxins for mammals. Aflatoxin production levels are reduced upon exposure to the volatile compounds methyl isovalerate and dimethyl disulfide, produced by the bacterium *Alcaligenes faecalis* N1–4, due to downregulation of the aflatoxin-biosynthesis genes (31).

While bacterial volatiles hold great promise for protecting our food supply from fungal spoilage, they can also adversely affect the growth/appearance of edible fungi. *Pseudomonas tolaasii* emits volatile compounds that cause blotch symptoms on many edible mushrooms (86). *P. tolaasii* also produces methanethiol, dimethyl disulfide, and 1-undecene, all of which have been associated with toxic effects on a variety of edible fungi (52).

3.2. Volatiles That Impact Bacterial Interactions with Protists

Beyond bacteria and fungi, protists are a major constituent of the soil microbiome, and as consumers of bacteria and fungi, they play an important role in shaping the microbial soil

community. Little is known about how protists sense their bacterial prey from a distance, but volatiles appear to be key factors. In response to volatile compounds emitted by six phylogenetically distinct bacteria, the soil protists *Saccamoeba lacustris*, *Tetramitus* sp., and *Vermamoeba vermiformis* significantly changed their activity, growth, and motility (81). Interestingly, protist activity differed in response to distinct soil bacteria. This implied that species-specific activity adaptations can be communicated by volatile signals (81). Recent work provides additional support for the idea that bacterial volatiles attract protists. Several volatile compounds, including decanal, 3,5-dimethylbenzaldehyde, and ethyl acetate emitted by *Listeria monocytogenes*, were found to attract the unicellular, flagellated protist *Euglena gracilis* (29). Collectively, these results suggest that volatile compounds may be a driving force for protist detection of possible bacterial food sources. It remains to be seen whether bacteria have also evolved volatile strategies to repel these predatory microbes.

3.3. Volatiles That Influence Arthropod Behavior

Arthropods encounter bacteria in their environment and establish symbiotic relationships with specific microbes. Increasingly, bacterial volatile compounds are being found to impact arthropod behavior and their competitive success (**Figure 1**).

3.3.1. Impact of volatiles from free-living bacteria. The African mosquito *Anopheles gambiae* Giles sensu stricto is one of the foremost vectors of malarial disease. These mosquitoes select their hosts on the basis of volatile compounds emitted by skin-associated bacteria (10), with different bacterial constituents influencing the relative attractiveness of that individual to mosquitoes. Human males whose skin harbors a highly diverse microbial community are less attractive to mosquitoes; lower bacterial diversity appears to attract the insects (99). Verhulst et al. (99) demonstrated that volatiles produced by *Staphylococcus epidermis* were more effective in recruiting mosquitoes compared with those produced by *P. aeruginosa*, and thus the relative proportion of each microbe can dictate the degree of attraction for *A. gambiae*. In terms of specific bacterial volatile compounds, butyl acetate, butyl 2-methylbutanoate, butyl butyrate, 3-methyl-1-butanol, 3-methylbutanoic acid, and dimethyl disulfide have all been shown to influence mosquito recruitment (98). These observations raise the tantalizing possibility of using volatiles to manipulate mosquito behavior, e.g., through the use of volatile traps to sequester mosquitoes away from people or volatile sprays as mosquito repellents, or by manipulating the skin microbiome (and its associated volatile repertoire) to reduce the risk of being bitten.

While recruiting mosquitoes through the release of volatile compounds confers no obvious benefit to the skin microbial population, other bacteria employ their volatile compounds for more advantageous purposes. The soil-dwelling *Streptomyces* bacteria are prolific volatile producers and are renowned for giving soil its earthy odor, courtesy of two volatile compounds: geosmin and 2-methylisoborneol (5, 35). These molecules are produced during the final stages of the classical *Streptomyces* life cycle, when the bacteria form dormant spores. Recent work has revealed geosmin, and 2-methylisoborneol to a lesser extent, attracts springtails. These microscopic arthropods both feast upon bacteria (including *Streptomyces* spores, which do not appear to be digested and are subsequently excreted) and serve as vectors for *Streptomyces* spore dispersal, through their adherence to the springtail surface (4). Interestingly, geosmin does not appear to be equally attractive to all arthropods, with *Drosophila* species being repelled by this volatile compound (89).

3.3.2. Impact of volatiles produced by symbiotic bacteria. Free-living bacteria make up the largest contingent of volatile producers that have been characterized to date, but increasingly,

volatiles are being found to play important roles in promoting and maintaining symbiotic relationships. A well-known microbe-insect symbiosis involves bark beetles and fungi. The fungal symbiont increases bark beetle fitness, and the beetle in turn serves as a transmission vector for the fungus. Bacteria are a third partner in this interaction network for many beetles. The red turpentine beetle *Dendroctonus valens* LeConte lives in symbiosis with the fungus *Leptographium procerum*, and with diverse bacterial species including *Rahnella aquatilis*, *Serratia liquefaciens*, and *Pseudomonas* sp. 7 B321. These bacteria generate a volatile cocktail, with one compound (ammonia) influencing fungal feeding behavior, stimulating their consumption of D-pinitol instead of glucose; glucose is thus reserved for consumption by the bacteria and the beetle. Beetle larvae living in association with these bacteria exhibited a significant weight increase relative to those without them, supporting the proposal that the bacteria are beneficial to the beetle (105). Another intriguing bacterial-beetle interaction has been noted for the harlequin ladybird beetle *Harmonia axyridis* (79). This insect uses the volatile compounds methylpyrazine and methoxypyrazine as antipredatory defense signals. Bacterial symbionts were identified as possible producers of these volatile compounds, and analysis of the beetle gut microbiome revealed abundant *Lactobacillus* and *Serratia* bacterial species, with both being known producers of the two antipredatory volatiles (79).

3.4. Bacterial Volatiles and Their Diverse Implications for Plants

The soil is home to not only a multitude of bacteria but also diverse fungi, protists, arthropods, and plants. For plants, interactions with bacteria can have beneficial or detrimental effects, and volatile compounds are now recognized as playing important roles in influencing these outcomes (**Figure 1**).

3.4.1. Impact of bacterial volatiles on plant pathogen growth. How bacterial volatiles affect plant growth is an area of active investigation. As traditional chemical treatments can be harmful to the environment and human health, the use of biocontrol strains as a more sustainable and environmentally friendly way to manage plant disease and promote plant growth is increasingly being explored. As described above, bacterial volatiles effectively inhibit the growth of both bacterial and fungal plant pathogens, and more directed and systematic strategies are now being pursued to understand the function of volatiles produced by biocontrol species and rhizosphere bacteria.

Several recent publications have reported on the ability of established biocontrol strains like *B. pumilus* (37, 60), *P. polymyxa* (73), *Bacillus velezensis* (13), *P. fluorescens* (106), and *Pseudomonas donghuensis* (62) to produce volatile compounds with antifungal activities. A promising strategy to accelerate the identification of beneficial volatile-producing bacteria has involved screening and analyzing members of the root and leaf microbiomes. Isolating endophytic bacteria from the roots of olive trees (13) and rhizobacteria from avocado trees (56) led to the identification of *B. velezensis* and a strain related to *Bacillus acidiceler*, both of which had large volatile repertoires (13, 56). These organisms were able to protect their associated trees from infection by the fungal pathogens *Fusarium solani* and *Phytophthora cinnamomi*, although it is not yet clear how much of this protection was due to antifungal volatiles, plant growth/defense promotion through volatile release or secretion of other secondary metabolites, or some other mechanism altogether.

In turning from trees to crop plants, analyzing the bacterial isolates associated with potato plants revealed >130 strains, with *Pseudomonas* species being the most represented (39). These strains were screened for antifungal activity, and those with inhibition capabilities were then tested for volatile activity against fungal pathogens. Exposing the potato blight–causing *Phytophthora infestans* to volatiles from five *Pseudomonas* strains led to full growth suppression (39). The alkene 1-undecene was the most abundant volatile produced by four of the five *Pseudomonas* strains. Adding

pure 1-undecene to the plant pathogen reduced mycelial growth and inhibited sporangium formation, germination, and zoospore release (39); however, it did not completely abrogate growth, suggesting that a volatile mixture is likely responsible for the antifungal activity observed. Subsequent investigations provided a more comprehensive definition of the volatile repertoire of these *Pseudomonas* strains. In addition to 1-undecene, these strains also produced abundant levels of dimethyl sulfide, 4-hydroxy-2-pentanone, and benzaldehyde, among other less abundant compounds. Testing of commercially available molecules revealed that many of them affected *P. infestans* growth and that most active compounds affected multiple stages of the fungal growth/developmental cycle (20).

In addition to the pseudomonads, streptomycetes have also been associated with plant protection. PhyloChip-based metagenomics of *R. solani* disease–suppressive soil revealed abundant actinobacteria, with an overrepresentation of *Streptomyces* species (16). Further analysis of select *Streptomyces* isolates revealed that these bacteria produced volatiles that could both reduce the hyphal growth of *R. solani* and promote the growth of *Arabidopsis thaliana* seedlings. Characterizing these volatile compounds ultimately led to the discovery of 1,3,5-trichloro-2-methoxy benzene, a compound produced by all tested *Streptomyces* species and that inhibited hyphal growth of *R. solani* (16). An independent investigation revealed caryolan-1-ol, a volatile compound produced by *Streptomyces* sp. S4–7, also had activity against a wide range of fungal plant pathogens, including *Botrytis cinerea*, *Colletotrichum gloeosporioides*, *F. oxysporum*, *Gibberella moniliformis*, *Phytophthora nicotianae*, *Rhizoctonia cerealis*, and *R. solani* (15). Caryolan-1-ol inhibits mycelial growth and is proposed to affect membrane lipid processes and intracellular transport systems (15). Finally, *Streptomyces fimicarius* BWL-H1 was found to emit several volatiles capable of inhibiting the growth of the downy blight–causing oomycete *Peronophythora litchi*. In defining the volatile profile of this streptomycete, researchers determined that phenylethyl alcohol was the most abundant compound within the 32 identified molecules. Commercially purchased phenylethyl alcohol and 7 other volatile compounds were tested, and all showed strong inhibitory activity against this oomycete (103). These studies collectively suggest that soil-dwelling bacteria have a vast volatile repertoire, with immense potential for biocontrol and fungal pathogen suppression.

3.4.2. Impact of bacterial volatiles on plant pathogen resistance. As described above, 2,3-butanediol can inhibit bacterial growth and influence biofilm formation and motility. Exposure to this volatile compound can also lead to improved pathogen resistance for *A. thaliana* (74). The positive effect of 2,3-butanediol on plant resistance appears to be broadly conserved. D'Alessandro et al. (18) discovered that maize seedlings could produce copious amounts of 2,3-butanediol, courtesy of the soil-derived endophytic bacterium *Enterobacteria aerogenes*, and that this volatile led to increased maize resistance to the corn leaf blight–causing fungus *Setosphaeria turcica* (18).

Fungal pathogens are also a scourge of the wine and grape industries. To probe the potential for bacterial control of fungal disease, grapevine stems were infected with the fungus *Phaeomoniella chlamydospora* and either treated with a fungicide or coinoculated with 1 of 46 strains of bacteria isolated from Bordeaux vineyards (37). Promisingly, bacterial treatment was equally effective as the fungicidal treatment of the plant in limiting the fungal infection. In follow-up experiments, two bacterial strains (*Paenibacillus* sp. and *B. pumilus*) were prophylactically inoculated, or inoculated alongside *P. chlamydospora* on grapevine cuttings. Irrespective of the inoculation method, both bacteria significantly reduced the extent of necrosis induced by the fungus (37). With the use of GC-MS, different pyrazines were found to be produced, with 2,5-dimethyl pyrazine identified as the major volatile compound produced by *B. pumilus*, and an unknown pyrazine, alongside less abundant 1-octen-3-ol and 2,6-bis-(2-methylpropyl) pyrazine, produced by the *Paenibacillus*

sp.; application of pure compound confirmed the inhibition of fungal growth and pathogen development. Interestingly, pretreatment of the plant with the bacteria induced the expression of genes involved in plant defense responses (37).

3.4.3. Direct influence of bacterial volatiles on plant growth. Volatile compounds that enhance plant growth can provide an environmentally friendly alternative to chemical fertilizers. These compounds can be produced by free-living bacteria in the rhizosphere, or by endophytic bacteria, and can benefit plants by, e.g., enhancing nutrient availability, inducing metabolic activities, and stimulating defense responses (65). 2,3-Butanediol and its precursor acetoin were among the first volatile compounds discovered to promote *A. thaliana* growth and induce its systemic defense response (26, 72, 74). Acetoin is produced by various bacterial species and has been additionally shown to increase lateral root numbers, increase dry weight, promote root growth, and enhance shoot length of lettuce (28). Following these promising initial discoveries, volatile-producing bacterial strains with plant growth–promoting effects continue to be identified (48, 71, 90). An intriguing example involves the endophytic bacterium *P. fluorescens* ALEB7B, which has been isolated from *Atractylodes lancea*, an important Chinese medicinal plant whose volatile oils are used in medicinal formulations (106). The bacterium cultured on its own emits the volatile, nitrogenous compounds formamide and N,N-dimethylformamide, alongside benzaldehyde, although only benzaldehyde could be detected following cocultivation of plant and bacterium. Application of pure formamide-based solutions led to improved plant growth, while pure benzaldehyde promoted oil accumulation (106).

Interestingly, bacteria identified in association with specific plants can have more promiscuous effects. For example, bacteria isolated from the rhizosphere, phyllosphere, and endosphere of agave and cacti could promote the growth of *A. thaliana* and *Nicotiana benthamiana* through their emission of volatile compounds (11). Most of the bacterial species had similar growth-promoting effects on both plants, suggesting that plants in general may respond similarly to these volatile/chemical signals. Characterizing the volatile repertoire of these agave- and cactus-associated bacteria revealed unexpected chemical diversity, including 10 novel volatile compounds (11). Application of pure aliquots of 2-phenyl alcohol and ethyl isovalerate led to substantial increases in the growth rate of *Agave tequilana* and *Agave salmiana* over a period of several months (11). This suggests that identifying beneficial volatile compounds and applying these to slow-growing and economically important plants could increase plant productivity and harvest yields.

How microbial volatiles exert their effects is a largely unanswered question. Recent mechanistic advances have, however, been made for *Microbacterium* species, whose volatile emissions serve to increase the root and shoot biomass of *A. thaliana*, tomato, and lettuce seedlings (17). Profiling of the associated volatiles revealed abundant sulfur-containing compounds, including dimethyl disulfide and dimethyl trisulfide. Dimethyl disulfide has previously been shown to support the growth of *Nicotiana attenuata* (55), alter the root system architecture of *A. thaliana* (increasing lateral root and root hair numbers) (93), and inhibit the growth of the fungal plant pathogen *B. cinerea* (71). In this study, dimethyl disulfide had no impact on *A. thaliana* shoot and root biomass production, while dimethyl trisulfide promoted concentration-dependent plant growth (17). Analysis of *Arabidopsis* gene expression in response to *Microbacterium* sp. volatiles as a whole unveiled the upregulation of an auxin receptor gene, alongside genes involved in the assimilation of sulfur and nitrogen and in sulfur biosynthesis and nitrogen transport (17). An independent study revealed that treating *A. thaliana* with dimethyl disulfide significantly increased the expression of several genes involved in auxin signaling (93), suggesting that root growth promotion by dimethyl disulfide may occur via the auxin signaling pathway.

3.5. Impact of Bacterial Volatiles on Higher Vertebrates

While plants obviously reap diverse benefits from their association with bacteria, bacterial communities are essential for the health and well-being of vertebrates as well (**Figure 1**). Microbes contribute to their host's immune response, behavior, nutrient uptake, and development. Connections between animal behavior and volatile chemical cues are increasingly being pieced together, in everything from birds to hyenas to humans.

Most birds secrete preen oil from their uropygial glands and apply this to enhance feather integrity, protect against parasites, attract mating partners, and repel rivals. Importantly, preen oil has a volatile component, and in some species, the presence of methyl ketones is correlated with reproductive success (101, 102). The uropygial glands are inhabited by symbiotic bacteria from diverse bacterial phyla (102). A subset of these bacteria could be cultivated from preen oil, and characterizing their volatile compendium unveiled the production of several linear alcohols (e.g., 1-dodecanol, 1-tridecanol), and, importantly, a variety of methyl ketones (e.g., 2-tridecanone, 2-tetradecanone, 2-pentadecanone) (102).

Key roles for gland-specific bacteria are not confined to avian species. Next-generation sequencing of the bacterial community living in scent glands of adult spotted and striped hyenas revealed an abundance of bacteria belonging to the fermentative, odor-producing *Clostridiales* order (91, 92). Different bacterial genera were, however, found within and between hyena species, and these were correlated with differences in volatile fatty acid profiles, and accompanying differences in the odors associated with gland secretions (92).

Short-chain fatty acids are also important volatile signals within the human microbiome. *Clostridia* and *Bacteroidia* are typical commensal inhabitants of the human gut, where they release short-chain fatty acids like butyrate, propionate, and acetate. Butyrate is the preferred energy source of colonocytes, and it influences colonic health by inhibiting proinflammatory reactions and protecting against colitis and colorectal cancer (23, 53). In general, short-chain fatty acids are thought to represent important communication signals between the intestinal microbiome and the human immune system (68), and it is likely that these represent a small fraction of the volatile-mediated processes driven by our commensal microbes.

4. BENEFITS AND DRAWBACKS OF VOLATILE MOLECULES

One of the greatest benefits afforded to bacteria from their use of volatile compounds is the propensity of these compounds to evaporate and their ability to diffuse through water, air, and soil. This allows these molecules to be readily dispersed, reaching areas and spanning distances that would be inaccessible to larger secondary metabolites. This enhances the extent of their impact, allowing the producer to communicate and compete with other organisms from a distance. At the same time, this means the effect of volatile compounds will be more diffuse, with greater production levels needed to achieve high local concentrations of these molecules, compared with less diffusible secondary metabolites.

The small size and relatively simple chemical nature of volatile compounds means that the genetic and energetic costs of producing them are far lower than for more complex secondary metabolites. Antibiotics, for example, require large biosynthetic gene clusters for their production; multiple enzymes are needed to assemble precursors and modify biosynthetic intermediates before yielding the final bioactive molecule (8, 19, 87). Conversely, the synthesis of most volatiles requires far fewer enzymes and modifications, and in some cases, they are emitted as by-products during the synthesis of more complex molecules (1, 6, 63).

The nature of their dispersal means that volatile compounds are common goods—all organisms in the vicinity can, in theory, access or sense these molecules. Whether this is an advantage or a

disadvantage to the producer organism likely depends upon the effect of the molecule on both the producer and its neighbors, and the energy required to produce it.

While they are simple compounds, volatile molecules can be challenging to study. Unlike secondary metabolites, their biosynthesis genes are not always easy to identify, and they can often be produced through multiple biochemical pathways. Consequently, pure solutions are often used in place of genetic experiments in assessing the importance or function of particular compounds. The diverse bouquet of volatile compounds produced by any one species also presents challenges in dissecting whether functional effects are the result of one or many volatile compounds.

5. LOOKING FORWARD—THE FUTURE IS UP IN THE AIR?

Bacterial volatiles are of increasing interest, and investigations into their production and function are on the rise. From their roles in shaping the environment and influencing nutrient availability to their impact on the growth and behavior of organisms of all types, the importance of these small molecules cannot be overstated. Identifying volatile compounds produced by bacteria is becoming more straightforward; understanding their function, determining how their effects are mediated, and uncovering the input signals and regulatory cascades governing their production are all important questions that remain open for investigation.

Beyond their fascinating biology, bacterial volatiles have outstanding translational potential. Given their antibacterial, antifungal, and adjuvant capabilities, there is tremendous scope to apply these molecules in clinical, agricultural, and industrial settings for use in controlling the growth, development, and toxicity of pathogenic microbes. Their ability to impact protist and arthropod/insect behavior is ripe for exploitation, paving the way to develop volatile strategies for attracting desirable insects and repelling deleterious ones. Understanding how bacterial volatiles promote plant, animal, and human health will open the door to new approaches to agricultural and medical practices and therapies. The future may well be volatile!

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LITERATURE CITED

1. Audrain B, Farag MA, Ryu C-M, Ghigo J-M. 2015. Role of bacterial volatile compounds in bacterial biology. *FEMS Microbiol. Rev.* 39:222–33
2. Avalos M, Garbeva P, Raaijmakers JM, van Wezel GP. 2020. Production of ammonia as a low-cost and long-distance antibiotic strategy by *Streptomyces* species. *ISME J.* 14(2):569–83
3. Avalos M, van Wezel GP, Raaijmakers JM, Garbeva P. 2018. Healthy scents: Microbial volatiles as new frontier in antibiotic research? *Curr. Opin. Microbiol.* 45:84–91
4. Becher PG, Verschut V, Bibb MJ, Bush MJ, Molnar BP, et al. 2020. Developmentally regulated volatiles geosmin and 2-methylisoborneol attract a soil arthropod to *Streptomyces* bacteria promoting spore dispersal. *Nat. Microbiol.* In press

5. Bentley SD, Chater KF, Cerdeño-Tárraga AM, Challis GL, Thomson NR, et al. 2002. Complete genome sequence of the model actinomycete *Streptomyces coelicolor* A3(2). *Nature* 417:141–47
6. Bernier SP, Létoffé S, Delepierre M, Ghigo J-M. 2011. Biogenic ammonia modifies antibiotic resistance at a distance in physically separated bacteria. *Mol. Microbiol.* 81:705–16
7. Bitas V, Kim H-S, Bennett JW, Kang S. 2013. Sniffing on microbes: diverse roles of microbial volatile organic compounds in plant health. *Mol. Plant Microbe Interact.* 26:835–43
8. Brakhage AA. 2013. Regulation of fungal secondary metabolism. *Nat. Rev. Microbiol.* 11:21–32
9. Briard B, Heddergott C, Latgé J-P. 2016. Volatile compounds emitted by *Pseudomonas aeruginosa* stimulate growth of the fungal pathogen *Aspergillus fumigatus*. *mBio* 7:e00219-16
10. Busula AO, Takken W, De Boer JG, Mukubana WR, Verhulst NO. 2017. Variation in host preferences of malaria mosquitoes is mediated by skin bacterial volatiles. *Med. Vet. Entomol.* 31:320–26
11. Camarena-Pozos DA, Flores-Núñez VM, López MG, López-Bucio J, Partida-Martínez LP. 2019. Smells from the desert: microbial volatiles that affect plant growth and development of native and non-native plant species. *Plant Cell Environ*. 42:1368–80
12. Čepl J, Blahůšková A, Cvrčková F, Markoš A. 2014. Ammonia produced by bacterial colonies promotes growth of ampicillin-sensitive *Serratia* sp. by means of antibiotic inactivation. *FEMS Microbiol. Lett.* 354:126–32
13. Cheffi M, Chenari Bouket A, Alenezi FN, Luptakova L, Belka M, et al. 2019. *Olea europaea* L. root endophyte *Bacillus velezensis* OEE1 counteracts oomycete and fungal harmful pathogens and harbours a large repertoire of secreted and volatile metabolites and beneficial functional genes. *Microorganisms* 7:314
14. Chen Y, Gozzi K, Yan F, Chai Y. 2015. Acetic acid acts as a volatile signal to stimulate bacterial biofilm formation. *mBio* 6:e00392-15
15. Cho G, Kim J, Park CG, Nislow C, Weller DM, Kwak Y-S. 2017. Caryolan-1-ol, an antifungal volatile produced by *Streptomyces* spp., inhibits the endomembrane system of fungi. *Open Biol.* 7:170075
16. Cordovez V, Carrion VJ, Etalo DW, Mumm R, Zhu H, et al. 2015. Diversity and functions of volatile organic compounds produced by *Streptomyces* from a disease-suppressive soil. *Front. Microbiol.* 6:1081
17. Cordovez V, Schop S, Hordijk K, de Boulois HD, Coppens F, et al. 2018. Priming of plant growth promotion by volatiles of root-associated *Microbacterium* spp. *Appl. Environ. Microbiol.* 84(22):e01865-18
18. D'Alessandro M, Erb M, Ton J, Brandenburg A, Karlen D, et al. 2014. Volatiles produced by soil-borne endophytic bacteria increase plant pathogen resistance and affect tritrophic interactions. *Plant Cell Environ*. 37:813–26
19. Davies J. 2013. Specialized microbial metabolites: functions and origins. *J. Antibiot.* 66:361–64
20. De Vrieze M, Pandey P, Bucheli TD, Varadarajan AR, Ahrens CH, et al. 2015. Volatile organic compounds from native potato-associated *Pseudomonas* as potential anti-oomycete agents. *Front. Microbiol.* 6:1295
21. Di Martino P, Fursy R, Bret L, Sundararaju B, Phillips RS. 2003. Indole can act as an extracellular signal to regulate biofilm formation of *Escherichia coli* and other indole-producing bacteria. *Can. J. Microbiol.* 49:443–49
22. Dickschat JS. 2010. Quorum sensing and bacterial biofilms. *Nat. Prod. Rep.* 27:343–69
23. Donohoe Dallas R, Garge N, Zhang X, Sun W, O'Connell TM, et al. 2011. The microbiome and butyrate regulate energy metabolism and autophagy in the mammalian colon. *Cell Metab.* 13:517–26
24. Effmert U, Kalderás J, Warnke R, Piechulla B. 2012. Volatile mediated interactions between bacteria and fungi in the soil. *J. Chem. Ecol.* 38:665–703
25. El-Halfawy OM, Valvano MA. 2013. Chemical communication of antibiotic resistance by a highly resistant subpopulation of bacterial cells. *PLOS ONE* 8:e68874
26. Farag MA, Ryu C-M, Sumner LW, Paré PW. 2006. GC–MS SPME profiling of rhizobacterial volatiles reveals prospective inducers of growth promotion and induced systemic resistance in plants. *Phytochemistry* 67:2262–68
27. Fiddaman PJ, Rossall S. 1993. The production of antifungal volatiles by *Bacillus subtilis*. *J. Appl. Microbiol.* 74:119–26
28. Fincheira P, Venthur H, Mutis A, Parada M, Quiroz A. 2016. Growth promotion of *Lactuca sativa* in response to volatile organic compounds emitted from diverse bacterial species. *Microbiol. Res.* 193:39–47

29. Gaines A, Ludovice M, Xu J, Zanghi M, Meinersmann RJ, et al. 2019. The dialogue between protozoa and bacteria in a microfluidic device. *PLOS ONE* 14:e0222484
30. Garbeva P, Hordijk C, Gerards S, de Boer W. 2014. Volatile-mediated interactions between phylogenetically different soil bacteria. *Front. Microbiol.* 5:289
31. Gong A-D, Wu N-N, Kong X-W, Zhang Y-M, Hu M-J, et al. 2019. Inhibitory effect of volatiles emitted from *Alcaligenes faecalis* N1–4 on *Aspergillus flavus* and aflatoxins in storage. *Front. Microbiol.* 10:1419
32. Groenhagen U, Baumgartner R, Bailly A, Gardiner A, Eberl L, et al. 2013. Production of bioactive volatiles by different *Burkholderia ambifaria* strains. *J. Chem. Ecol.* 39:892–906
33. Gusarov I, Nudler E. 2005. NO-mediated cytoprotection: Instant adaptation to oxidative stress in bacteria. *PNAS* 102:13855–60
34. Gusarov I, Shatalin K, Starodubtseva M, Nudler E. 2009. Endogenous nitric oxide protects bacteria against a wide spectrum of antibiotics. *Science* 325:1380–84
35. Gust B, Challis GL, Fowler K, Kieser T, Chater KF. 2003. PCR-targeted *Streptomyces* gene replacement identifies a protein domain needed for biosynthesis of the sesquiterpene soil odor geosmin. *PNAS* 100:1541–46
36. Hagai E, Dvora R, Havkin-Blank T, Zelinger E, Porat Z, et al. 2014. Surface-motility induction, attraction and hitchhiking between bacterial species promote dispersal on solid surfaces. *ISME J.* 8:1147–51
37. Haidar R, Roudet J, Bonnard O, Dufour MC, Corio-Costet MF, et al. 2016. Screening and modes of action of antagonistic bacteria to control the fungal pathogen *Phaeomoniella chlamydospora* involved in grapevine trunk diseases. *Microbiol. Res.* 192:172–84
38. Herrington PR, Craig JT, Sheridan JE. 1987. Methyl vinyl ketone: a volatile fungistatic inhibitor from *Streptomyces griseoruber*. *Soil Biol. Biochem*. 19:509–12
39. Hunziker L, Bonisch D, Groenhagen U, Bailly A, Schulz S, Weisskopf L. 2015. *Pseudomonas* strains naturally associated with potato plants produce volatiles with high potential for inhibition of *Phytophthora infestans*. *Appl. Environ. Microbiol*. 81:821–30
40. Insam H, Seewald MSA. 2010. Volatile organic compounds (VOCs) in soils. *Biol. Fertil. Soils* 46:199–213
41. Janssens TKS, Tyc O, Besselink H, de Boer W, Garbeva P. 2019. Biological activities associated with the volatile compound 2,5-bis(1-methylethyl)-pyrazine. *FEMS Microbiol. Lett.* 366:fnz023
42. Jones SE, Elliot MA. 2018. 'Exploring' the regulation of *Streptomyces* growth and development. *Curr. Opin. Microbiol.* 42:25–30
43. Jones SE, Ho L, Rees CA, Hill JE, Nodwell JR, Elliot MA. 2017. *Streptomyces* exploration is triggered by fungal interactions and volatile signals. *eLife* 6:e21738
44. Jones SE, Pham CA, Zambri MP, McKillip J, Carlson EE, Elliot MA. 2019. *Streptomyces* volatile compounds influence exploration and microbial community dynamics by altering iron availability. *mBio* 10:e00171-19
45. Kai M, Effmert U, Piechulla B. 2016. Bacterial-plant-interactions: approaches to unravel the biological function of bacterial volatiles in the rhizosphere. *Front. Microbiol.* 7:108
46. Kanchiswamy CN, Malnoy M, Maffei ME. 2015. Chemical diversity of microbial volatiles and their potential for plant growth and productivity. *Front. Plant Sci.* 6:151
47. Kim K-S, Lee S, Ryu C-M. 2013. Interspecific bacterial sensing through airborne signals modulates locomotion and drug resistance. *Nat. Commun.* 4:1809
48. Ledger T, Rojas S, Timmermann T, Pinedo I, Poupin MJ, et al. 2016. Volatile-mediated effects predominate in *Paraburkholderia phytofirmans* growth promotion and salt stress tolerance of *Arabidopsis thaliana*. *Front. Microbiol*. 7:1838
49. Lee J-H, Lee J. 2010. Indole as an intercellular signal in microbial communities. *FEMS Microbiol. Rev.* 34:426–44
50. Lemfack MC, Ravella SR, Lorenz N, Kai M, Jung K, et al. 2016. Novel volatiles of skin-borne bacteria inhibit the growth of Gram-positive bacteria and affect quorum-sensing controlled phenotypes of Gram-negative bacteria. *Syst. Appl. Microbiol.* 39:503–15
51. Létoffé S, Audrain B, Bernier SP, Delepierre M, Ghigo J-M. 2014. Aerial exposure to the bacterial volatile compound trimethylamine modifies antibiotic resistance of physically separated bacteria by raising culture medium pH. *mBio* 5:e00944-13

52. Lo Cantore P, Giorgio A, Iacobellis NS. 2015. Bioactivity of volatile organic compounds produced by *Pseudomonas tolaasii*. *Front. Microbiol*. 6:1082
53. Lopetuso LR, Scaldaferri F, Petito V, Gasbarrini A. 2013. Commensal Clostridia: leading players in the maintenance of gut homeostasis. *Gut Pathog*. 5:23
54. McCain AH. 1966. A volatile antibiotic produced by *Streptomyces griseus*. *Phytopathology* 56:150
55. Meldau DG, Meldau S, Hoang LH, Underberg S, Wünsche H, Baldwin IT. 2013. Dimethyl disulfide produced by the naturally associated bacterium *Bacillus* sp B55 promotes *Nicotiana attenuata* growth by enhancing sulfur nutrition. *Plant Cell* 25:2731–47
56. Méndez-Bravo A, Cortazar-Murillo EM, Guevara-Avendaño E, Ceballos-Luna O, Rodríguez-Haas B, et al. 2018. Plant growth-promoting rhizobacteria associated with avocado display antagonistic activity against *Phytophthora cinnamomi* through volatile emissions. *PLOS ONE* 13:e0194665
57. Misztal PK, Lymperopoulou DS, Adams RI, Scott RA, Lindow SE, et al. 2018. Emission factors of microbial volatile organic compounds from environmental bacteria and fungi. *Environ. Sci. Technol.* 52:8272–82
58. Molina-Santiago C, Daddaoua A, Fillet S, Duque E, Ramos J-L. 2014. Interspecies signalling: *Pseudomonas putida* efflux pump TtgGHI is activated by indole to increase antibiotic resistance. *Environ. Microbiol.* 16:1267–81
59. Montes Vidal D, von Rymon-Lipinski A-L, Ravella S, Groenhagen U, Herrmann J, et al. 2017. Long-chain alkyl cyanides: unprecedented volatile compounds released by *Pseudomonas* and *Micromonospora* bacteria. *Angew. Chem. Int. Ed. Engl.* 56:4342–46
60. Morita T, Tanaka I, Ryuda N, Ikari M, Ueno D, Someya T. 2019. Antifungal spectrum characterization and identification of strong volatile organic compounds produced by *Bacillus pumilus* TM-R. *Heliyon* 5:e01817
61. Nijland R, Burgess JG. 2010. Bacterial olfaction. *Biotechnol. J.* 5:974–77
62. Ossowicki A, Jafra S, Garbeva P. 2017. The antimicrobial volatile power of the rhizospheric isolate *Pseudomonas donghuensis* P482. *PLOS ONE* 12:e0174362
63. Peñuelas J, Asensio D, Tholl D, Wenke K, Rosenkranz M, et al. 2014. Biogenic volatile emissions from the soil. *Plant Cell Environ*. 37:1866–91
64. Piechulla B, Lemfack MC, Kai M. 2017. Effects of discrete bioactive microbial volatiles on plants and fungi. *Plant Cell Environ*. 40:2042–67
65. Ping L, Boland W. 2004. Signals from the underground: Bacterial volatiles promote growth in *Arabidopsis*. *Trends Plant Sci*. 9:263–66
66. Plyuta V, Lipasova V, Popova A, Koksharova O, Kuznetsov A, et al. 2016. Influence of volatile organic compounds emitted by *Pseudomonas* and *Serratia* strains on *Agrobacterium tumefaciens* biofilms. *APMIS* 124:586–94
67. Que Y-A, Hazan R, Strobel B, Maura D, He J, et al. 2013. A quorum sensing small volatile molecule promotes antibiotic tolerance in bacteria. *PLOS ONE* 8:e80140
68. Ratajczak W, Ryl A, Mizerski A, Walczakiewicz K, Sipak O, Laszczynska M. 2019. Immunomodulatory potential of gut microbiome-derived short-chain fatty acids (SCFAs). *Acta Biochim. Pol.* 66:1–12
69. Raza W, Ling N, Liu D, Wei Z, Huang Q, Shen Q. 2016. Volatile organic compounds produced by *Pseudomonas fluorescens* WR-1 restrict the growth and virulence traits of *Ralstonia solanacearum*. *Microbiol. Res*. 192:103–13
70. Raza W, Wang J, Wu Y, Ling N, Wei Z, et al. 2016. Effects of volatile organic compounds produced by *Bacillus amyloliquefaciens* on the growth and virulence traits of tomato bacterial wilt pathogen *Ralstonia solanacearum*. *Appl. Microbiol. Biotechnol*. 100:7639–50
71. Rojas-Solís D, Zetter-Salmón E, Contreras-Pérez M, Rocha-Granados MDC, Macías-Rodríguez L, Santoyo G. 2018. *Pseudomonas stutzeri* E25 and *Stenotrophomonas maltophilia* CR71 endophytes produce antifungal volatile organic compounds and exhibit additive plant growth-promoting effects. *Biocatal. Agric. Biotechnol.* 13:46–52
72. Rudrappa T, Biedrzycki ML, Kunjeti SG, Donofrio NM, Czymmek KJ, et al. 2010. The rhizobacterial elicitor acetoin induces systemic resistance in *Arabidopsis thaliana*. *Commun. Integr. Biol*. 3:130–38
73. Rybakova D, Rack-Wetzlinger U, Cernava T, Schaefer A, Schmuck M, Berg G. 2017. Aerial warfare: a volatile dialogue between the plant pathogen *Verticillium longisporum* and its antagonist *Paenibacillus polymyxa*. *Front. Plant Sci*. 8:1294

74. Ryu C-M, Farag MA, Hu C-H, Reddy MS, Kloepper JW, Paré PW. 2004. Bacterial volatiles induce systemic resistance in *Arabidopsis*. *Plant Physiol*. 134:1017–26
75. Sagar NM, Cree IA, Covington JA, Arasaradnam RP. 2015. The interplay of the gut microbiome, bile acids, and volatile organic compounds. *Gastroenterol. Res. Pract.* 2015:398585
76. Schenkel D, Lemfack M, Piechulla B, Splivallo R. 2015. A meta-analysis approach for assessing the diversity and specificity of belowground root and microbial volatiles. *Front. Plant Sci.* 6:707
77. Schmidt R, Cordovez V, de Boer W, Raaijmakers J, Garbeva P. 2015. Volatile affairs in microbial interactions. *ISME J.* 9:2329–35
78. Schmidt R, Etalo DW, de Jager V, Gerards S, Zweers H, et al. 2016. Microbial small talk: volatiles in fungal–bacterial interactions. *Front. Microbiol.* 6:1495
79. Schmidtberg H, Shukla SP, Halitschke R, Vogel H, Vilcinskas A. 2019. Symbiont-mediated chemical defense in the invasive ladybird *Harmonia axyridis*. *Ecol. Evol*. 9:1715–29
80. Schulz S, Dickschat JS. 2007. Bacterial volatiles: the smell of small organisms. *Nat. Prod. Rep.* 24:814–42
81. Schulz-Bohm K, Geisen S, Wubs ERJ, Song C, de Boer W, Garbeva P. 2017. The prey's scent—volatile organic compound mediated interactions between soil bacteria and their protist predators. *ISME J.* 11:817–20
82. Schulz-Bohm K, Martín-Sánchez L, Garbeva P. 2017. Microbial volatiles: small molecules with an important role in intra- and inter-kingdom interactions. *Front. Microbiol.* 8:2484
83. Schulz-Bohm K, Zweers H, de Boer W, Garbeva P. 2015. A fragrant neighborhood: volatile mediated bacterial interactions in soil. *Front. Microbiol.* 6:1212
84. Scott J, Sueiro-Olivares M, Ahmed W, Heddergott C, Zhao C, et al. 2019. *Pseudomonas aeruginosa*-derived volatile sulfur compounds promote distal *Aspergillus fumigatus* growth and a synergistic pathogen-pathogen interaction that increases pathogenicity in co-infection. *Front. Microbiol.* 10:2311
85. Shatalin K, Shatalina E, Mironov A, Nudler E. 2011. H_2S: a universal defense against antibiotics in bacteria. *Science* 334:986–90
86. Shirata A. 1996. Production of volatile components by *Pseudomonas tolaasii* and their toxic activity. *Jpn. J. Phytopathol.* 62:185–93
87. Smith DJ, Burnham MK, Bull JH, Hodgson JE, Ward JM, et al. 1990. Beta-lactam antibiotic biosynthetic genes have been conserved in clusters in prokaryotes and eukaryotes. *EMBO J.* 9:741–47
88. Spraker JE, Jewell K, Roze LV, Scherf J, Ndagano D, et al. 2014. A volatile relationship: profiling an inter-kingdom dialogue between two plant pathogens, *Ralstonia solanacearum* and *Aspergillus flavus*. *J. Chem. Ecol*. 40:502–13
89. Stensmyr MC, Dweck Hany KM, Farhan A, Ibba I, Strutz A, et al. 2012. A conserved dedicated olfactory circuit for detecting harmful microbes in *Drosophila*. *Cell* 151:1345–57
90. Tahir HAS, Gu Q, Wu H, Raza W, Safdar A, et al. 2017. Effect of volatile compounds produced by *Ralstonia solanacearum* on plant growth promoting and systemic resistance inducing potential of *Bacillus* volatiles. *BMC Plant Biol*. 17:133
91. Theis KR, Schmidt TM, Holekamp KE. 2012. Evidence for a bacterial mechanism for group-specific social odors among hyenas. *Sci. Rep.* 2:615
92. Theis KR, Venkataraman A, Dycus JA, Koonter KD, Schmitt-Matzen EN, et al. 2013. Symbiotic bacteria appear to mediate hyena social odors. *PNAS* 110:19832–37
93. Tyagi S, Kim K, Cho M, Lee KJ. 2019. Volatile dimethyl disulfide affects root system architecture of *Arabidopsis* via modulation of canonical auxin signaling pathways. *Environ. Sustainability* 2:211–16
94. Tyc O, de Jager VCL, van den Berg M, Gerards S, Janssens TKS, et al. 2017. Exploring bacterial interspecific interactions for discovery of novel antimicrobial compounds. *Microb. Biotechnol.* 10:910–25
95. Tyc O, Zweers H, de Boer W, Garbeva P. 2015. Volatiles in inter-specific bacterial interactions. *Front. Microbiol.* 6:1412
96. Venkataraman A, Rosenbaum MA, Werner JJ, Winans SC, Angenent LT. 2014. Metabolite transfer with the fermentation product 2,3-butanediol enhances virulence by *Pseudomonas aeruginosa*. *ISME J.* 8:1210–20
97. Veraart AJ, Garbeva P, van Beersum F, Ho A, Hordijk CA, et al. 2018. Living apart together—bacterial volatiles influence methanotrophic growth and activity. *ISME J.* 12:1163–66

98. Verhulst NO, Andriessen R, Groenhagen U, Bukovinszkiné Kiss G, Schulz S, et al. 2011. Differential attraction of malaria mosquitoes to volatile blends produced by human skin bacteria. *PLOS ONE* 5:e15829
99. Verhulst NO, Qiu YT, Beijleveld H, Maliepaard C, Knights D, et al. 2011. Composition of human skin microbiota affects attractiveness to malaria mosquitoes. *PLOS ONE* 6:e28991
100. Werner S, Polle A, Brinkmann N. 2016. Belowground communication: impacts of volatile organic compounds (VOCs) from soil fungi on other soil-inhabiting organisms. *Appl. Microbiol. Biotechnol.* 100:8651–65
101. Whittaker DJ, Gerlach NM, Soini HA, Novotny MV, Ketterson ED. 2013. Bird odour predicts reproductive success. *Anim. Behav.* 86:697–703
102. Whittaker DJ, Slowinski SP, Greenberg JM, Alian O, Winters AD, et al. 2019. Experimental evidence that symbiotic bacteria produce chemical cues in a songbird. *J. Exp. Biol.* 222:jeb202978
103. Xing M, Zheng L, Deng Y, Xu D, Xi P, et al. 2018. Antifungal activity of natural volatile organic compounds against litchi downy blight pathogen *Peronophythora litchii*. *Molecules* 23:358
104. Zetola NM, Modongo C, Matsiri O, Tamuhla T, Mbongwe B, et al. 2017. Diagnosis of pulmonary tuberculosis and assessment of treatment response through analyses of volatile compound patterns in exhaled breath samples. *J. Infect.* 74:367–76
105. Zhou F, Xu L, Wang S, Wang B, Lou Q, et al. 2017. Bacterial volatile ammonia regulates the consumption sequence of D-pinitol and D-glucose in a fungus associated with an invasive bark beetle. *ISME J.* 11:2809–20
106. Zhou J-Y, Li X, Zheng J-Y, Dai C-C. 2016. Volatiles released by endophytic *Pseudomonas fluorescens* promoting the growth and volatile oil accumulation in *Atractylodes lancea*. *Plant Physiol. Biochem.* 101:132–40
107. Zou C-S, Mo M-H, Gu Y-Q, Zhou J-P, Zhang K-Q. 2007. Possible contributions of volatile-producing bacteria to soil fungistasis. *Soil Biol. Biochem.* 39:2371–79