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Healthy scents: microbial volatiles as new frontier in antibiotic research?

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Microorganisms represent a large and still resourceful pool for the discovery of novel compounds to combat antibiotic resistance in human and animal pathogens. The ability of microorganisms to produce structurally diverse volatile compounds has been known for decades, yet their biological functions and antimicrobial activities have only recently attracted attention. Various studies revealed that microbial volatiles can act as infochemicals in long-distance cross-kingdom communication as well as antimicrobials in competition and predation. Here, we review recent insights into the natural functions and modes of action of microbial volatiles and discuss their potential as a new class of antimicrobials and modulators of antibiotic resistance.

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Introduction: the problem of antimicrobial resistance

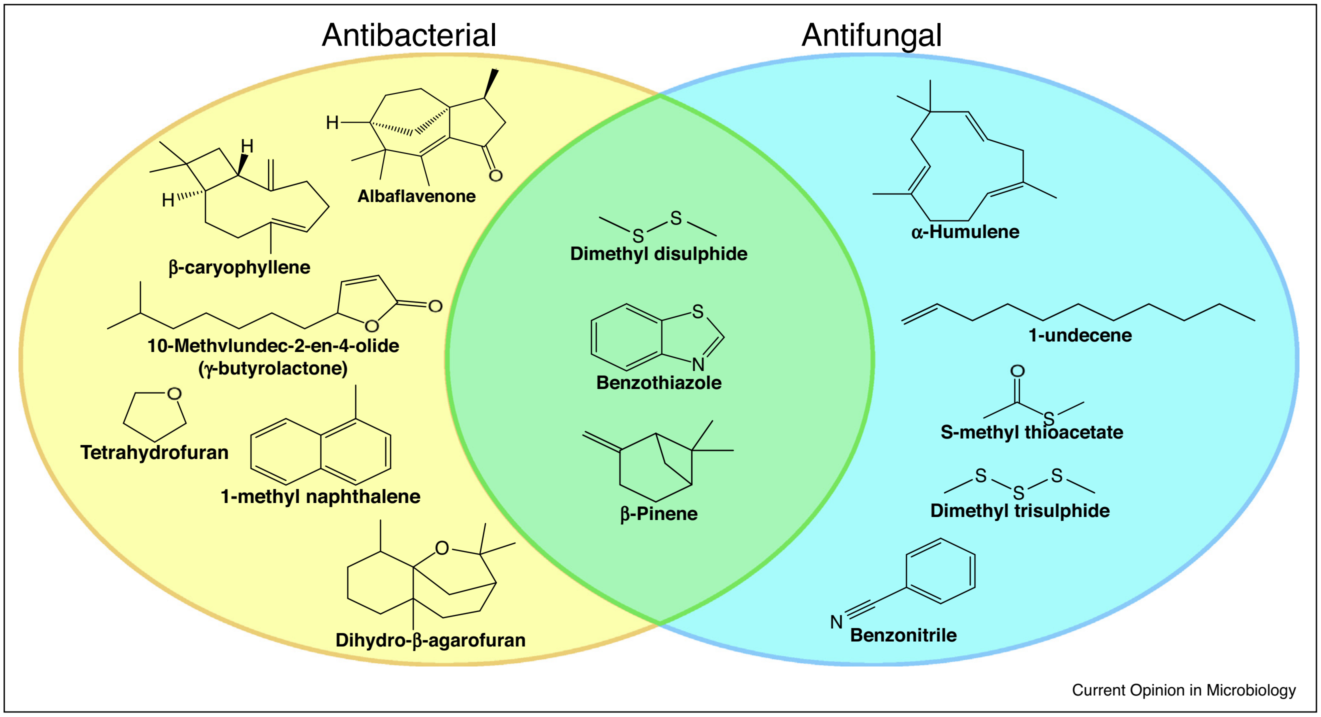
The discovery and use of antibiotics to treat infectious diseases has dramatically affected human life spans. Nevertheless, the increasing use of antibiotics has led to a rapid acquisition of antibiotic resistance by pathogenic microorganisms [1,2] as was already predicted by Alexander Fleming shortly after he discovered penicillin [3]. The threat of the increased frequency of antibiotic resistance is further augmented by the reduced interest and efforts of the pharmaceutical industry to discover and develop novel antibiotics [4–6]. Therefore, scientists are taking the lead in finding new strategies to identify new antibiotics to turn the tide of antibiotic-resistance [7]. In particular, we need to expand the chemical space of bioactive molecules with different modes of action and for which resistance development is less likely to occur. To date, the attention of industrial screening efforts has been almost exclusively directed at canonical antibiotic classes such as polyketides (PKS), nonribosomal (NRPS) and ribosomal (RiPP) peptide antibiotics, β-lactams and aminoglycosides. However, there is a major and highly diverse class of natural products that has been largely ignored by the pharmaceutical industry, namely the volatile compounds. Research on microbial volatiles is an emerging field with immense potential for both human, animal and plant health [8–11]. Here, we provide a brief and up-to-date overview of recent studies concerning the natural functions of microbial volatiles with a specific focus on volatiles that have antimicrobial activity or that act as modulators of antimicrobial resistance.

Chemical diversity and natural functions of microbial volatile compounds (MVCs)

Bacteria and fungi release a plethora of organic and inorganic volatile compounds, small molecules with low molecular weight and high vapour pressure. These physicochemical properties enable MVCs to diffuse more easily, allowing dispersal over longer distances than other microbial metabolites. A decade ago, the excellent review by Schulz and Dickschat [12••] on microbial volatiles marked the rise of this emerging and exciting research field of natural product chemistry. Since then, numerous structurally diverse MVCs produced by marine and terrestrial microorganisms have been described [13,14]. MVCs belong to diverse chemical classes, including alkanes, alkenes, alcohols, esters, ketones, terpenoids, sulfur-containing compounds and a range of small inorganic compounds. Moreover, within these classes there appears to be an enormous chemical diversity of MVCs that remains to be discovered as exemplified by the terpenes sodorifen [15] and pristinol [16•]. MVCs may be unique to a single phylogenetic group or even species, which also allows the use of MVCs for chemotaxonomic purposes [17] and for the selective detection of pathogens in both indoor and outdoor environments [18]. For example, VCs produced by *Mycobacterium tuberculosis* help to detect the pulmonary infection and asses the efficacy of treatment [19] (Figure 1).

MVCs play important ecological roles in intra-kingdom and inter-kingdom interactions [20,21•]. Activities

Figure 1



Examples of MVCs with antimicrobial activity.

reported for MVCs include modulation of growth, motility, virulence and biofilm formation as well as production of specialized metabolites (e.g. toxins), antibiotic resistance and spore germination in competing microorganisms (i.e. bacteria, fungi) [22,23,24•,25–27]. For example, some *Streptomyces* species surpass obstacles by so-called 'explorer cells', whereby they colonize new areas in the face of competition induced by the biogenic volatile trimethylamine [28•]. The skin-borne *Staphyloccoccus schleiferi* produces schleiferons A and B that modulate the skin microbiome possibly by inhibiting the growth of Gram-positive bacteria and by interfering with prodiginines production [26]. Plants also respond to and utilize MVCs leading to growth promotion or inhibition, induced systemic resistance or alteration of the plant metabolome [11,29,30]. Recent studies further point to other intriguing ecological roles of MVCs in cross-kingdom interactions. For example, ammonia produced by bacteria promotes the symbiosis between a fungus and a beetle by regulating the consumption sequence of the carbon sources pinitol and glucose [31]. Other studies indicated that volatiles from *Bacillus subtilis Pseudomonas fluorescens*, *Serratia odorifera*, and *Xanthomonas campestris* act as infochemicals disclosing a food source to bacterial predators, whereby the nematode *Caenorhabditis elegans* responded by crossing a 3-cm plastic barrier presumably to feed on the bacteria [9]. By contrast, MVCs like acetaldehyde, cyclohexene and dimethyl disulfide, were reported to reduce the motility of nematodes [32]. Recent studies in our labs further revealed that terpenes from *Collimonas* may act as a defense mechanism against protozoan predation [21•]. Also the terpene geosmin produced by *Streptomyces* and other bacteria has been proposed to be multifunctional as a signalling molecule involved in sporulation of the producing strain [33] and as a deterrent in food for *Drosophila* flies [34]. For more comprehensive overviews of other natural roles of MVCs in intra-specific and interspecific interactions and cross-kingdom communication, we refer to several recent reviews [9,14,35,36••,37–39].

Microbial volatile compounds as antimicrobials

MVCs can have significant inhibitory effects on the growth or development of other microorganisms (Figure 2). The activity spectrum of MVCs appears to be as diverse as their chemistry. Most of the studies to date have focused on antifungal activities of MVCs and only a few have reported their antibacterial properties. Examples include: the hormone-like γ-butyrolactones with broad spectrum activity against bacteria, fungi and yeast [13]; furfuryl isovalerate that inhibits growth of Gram-positive and Gram-negative bacteria, and acts as a quorum quencher in Gram-negative bacteria [13]; pyrazines (2,5-bis(1-methylethyl)-pyrazine), produced by *Paenibacillus* in interaction with *Burkholderia* [40], with activity against human pathogenic bacteria like