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Review

Fungal volatile organic compounds: A review with emphasis on their biotechnological potential

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ABSTRACT

Fungi produce various mixtures of gas-phase, carbon-based compounds called volatile organic compounds (VOCs) that due to their small size are able to diffuse through the atmosphere and soils. Despite some methodological and technological constraints, researchers have detected and characterized approximately 250 fungal VOCs, many of which have characteristic odors and are produced during primary and secondary metabolism. Fungal VOCs may contribute to a controversial medical diagnosis called “sick building syndrome” and may also be important in the success of some biocontrol species of *Trichoderma*. VOCs also play important signaling roles for fungi in their natural environments. Many ecological interactions are mediated by VOCs, including those between fungi and plants, arthropods, bacteria, and other fungi. The diverse functions of fungal VOCs can be developed for use in biotechnological applications for biofuel, biocontrol, and mycofumigation. Volatiles represent a new frontier in bioprospecting, and the study of these gas-phase compounds promises the discovery of new products for human exploitation and will generate new hypotheses in fundamental biology.

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1. Introduction to fungal volatile organic compounds

Volatile organic compounds (VOCs) are carbon-based solids and liquids that readily enter the gas phase by vaporizing at 0.01 kPa at a temperature of approximately 20 °C (Pagans *et al.*, 2006). Most are lipid soluble and thus have low water solubility. Approximately 250 VOCs have been identified from fungi where they occur as mixtures of simple hydrocarbons, heterocycles, aldehydes, ketones, alcohols, phenols, thioalcohols, thioesters and their derivatives, including, among others, benzene derivatives, and cyclohexanes (Chiron and Michelot, 2005; Korpi *et al.*, 2009; Ortiz-Castro *et al.*, 2009). Fungal VOCs are derived from both primary and secondary metabolism pathways (Korpi *et al.*, 2009), and because VOCs

can diffuse through the atmosphere and soil, they are ideal “infochemicals” (Table 1).

Many VOCs have distinctive odors so it is not surprising that interest in fungal VOCs began with the fungi that humans can smell. For example, the distinct bouquets of macrofungi such as mushrooms and truffles, highly valued in the culinary arts, include mixtures of different VOCs, of which alcohols, aldehydes, terpenes, aromatics and thiols dominate (Breheret *et al.*, 1997; Tirillini *et al.*, 2000; Splivallo *et al.*, 2007b; Cho *et al.*, 2008; Fraatz and Zorn, 2010). Moreover, the musty odor of fungal VOCs emitted from microscopic fungi is easily recognized in damp moldy buildings and has provided a foundation for studies that investigate the possible negative effects of molds on human health, in what is often referred to as “sick building syndrome”. Predominate in this

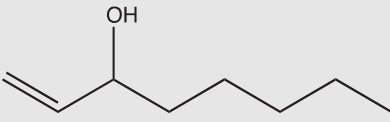
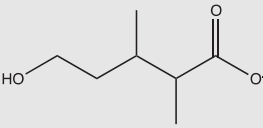
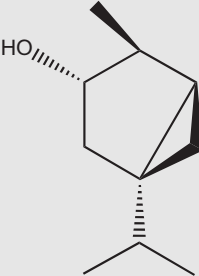
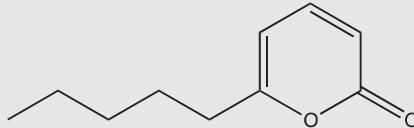
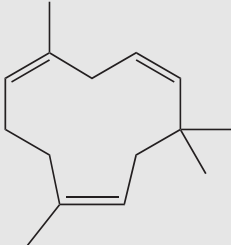
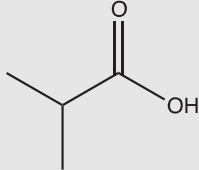
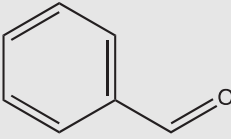
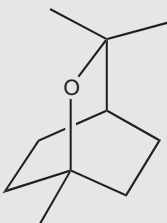
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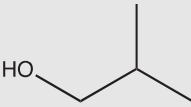
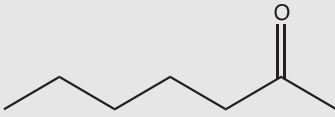
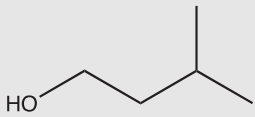
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Table 1 – Structures, functions and odors of selected common volatile compounds produced by fungi.

Molecule	Structure	Potential Function(s); odors
1-Octen-3-ol		Semiochemical; earthy, "mushroomy" odor
1-Butanol-3-, methyl-, acetate		Antifungal; banana odor
Sabinene		Unknown; peppery odor
6-Pentyl- α -pyrone		Antibiotic; coconut odor
β -Caryophyllene		Plant-growth promoting; woody-spicy odor
Isobutyric acid		Antifungal; rancid cheese-like odor
Benzyl aldehyde		Anti-microbial; almond odor
1,8-Cineole		Antifungal; camphor-like odor

Molecule	Structure	Potential Function(s); odors
2-Methyl-1-propanol		Fungivore attractant; mild alcohol odor
2-Heptanone		Unknown; cheese odor
3-Methyl-butanol		Unknown; component of truffle odor

musty odor are eight carbon compounds such as 1-octen-3-ol and 3-octanone (Morey *et al.*, 1997). Chemical ecologists have elucidated the role of many fungal VOCs as semiochemicals that function as attractants and deterrents to insects and other invertebrates. In agriculture, fungal VOCs have been used as part of biological control strategies to prevent the growth of plant pathogens. Additionally, there is increasing interest in the study of the plant-growth promoting effects of these VOC mixtures. In the food industry, the same biological control properties are used to prevent post-harvest fungal growth, in what is termed “mycofumigation”. Most recently, fungal VOCs have been studied for their potential role as fuel sources, popularly referred to as “mycodiesel”.

A single review cannot do justice to the enormous scientific literature that has contributed to our current knowledge about fungal VOCs (see Fig 1). Therefore, this paper will focus on recent improvements in our ability to isolate and identify VOCs, as well as on provocative new findings in toxicology and biocontrol from the study of endophytes that highlight the physiological potency of these small gas-phase molecules and their potential for exploitation in biotechnology. For an overview of the contributions of fungal VOCs to food and flavor research see (Chiron and Michelot, 2005; Fraatz and Zorn, 2010; Styger *et al.*, 2011).

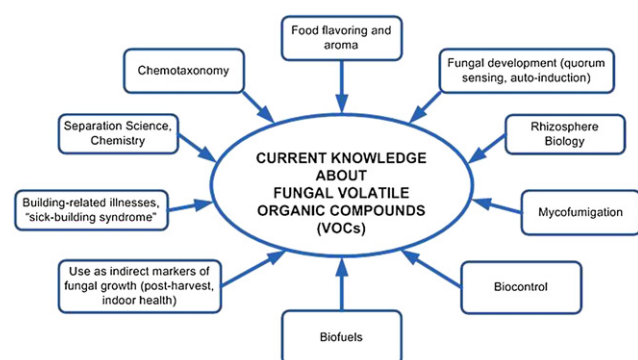


Fig 1 – Subdisciplines that have contributed to our knowledge of fungal VOCs.

2. Fungal VOC collection and detection

The study of fungal volatiles has lagged behind the study of other fungal metabolites due to methodological and technological constraints. Moreover, VOC production is biologically dynamic. The VOC profile of a given species or strain will vary depending on the substrate, duration of incubation, type of nutrients, temperature, and other environmental parameters (Pasanen *et al.*, 1997; Nilsson *et al.*, 2004; Fiedler *et al.*, 2005). With these constraints in mind, the methods currently in use are summarized briefly here.

Over the last half-century, there has been significant progress in “separation science”. Currently, gas chromatography–mass spectrometry (GC–MS), due to its powerful separation and highly sensitive detection capabilities, is the main method for detecting fungal VOCs (Matysik *et al.*, 2009). The culture headspace can be concentrated using solid adsorbents such as Tenax, followed by thermal desorption into the GC–MS. Compounds are then identified using a library or database of mass spectra, or by comparison of retention times and spectra with those of known standards. Another method of adsorbing and desorbing VOCs in culture headspace is *via* solid-phase microextraction (SPME), where desorption occurs in the GC injector itself. SPME has become increasingly popular in recent years because it reduces preparation time by combining extraction, concentration and introduction into one step while increasing sensitivity over other extraction methods (Zhang and Li, 2010). Additionally, Headspace-SPME GC–MS can be automated for direct profiling of living fungal cultures (Stoppacher *et al.*, 2010). However, one limitation of GC–MS is that it cannot be used for the identification of novel compounds.

Using activated charcoal filters, Matysik *et al.* (2009) demonstrated a proficiency in adsorbing hydrocarbons, esters, ethers, alcohols, ketones, glycol ethers and halogenated hydrocarbons. However, less volatile compounds and reactive compounds such as amines, phenols, aldehydes, and unsaturated hydrocarbons were not recovered efficiently due to their strong adsorption. The VOCs were desorbed from

the activated charcoal pads with 1.5 mL carbon disulfide and the extract decanted into the GC vials for GC–MS analysis (Matysik et al., 2009). This passive sampling method combined with GC–MS was applied for the detection of microbial volatile organic compounds (MVOCs) emitted by fungal species in the genera *Penicillium*, *Aspergillus*, and *Cladosporium* (Matysik et al., 2009).

The more traditional method of simultaneous distillation extraction (SDE) combines vapor distillation and solvent extraction. SDE has been used to examine the VOCs of *Penicillium roqueforti* and to compare the method to SPME (Jeleń, 2003). However, an earlier study comparing methods of analyzing the VOCs of *Penicillium vulpinum* found that SDE was inadequate to determine a full volatile profile when compared to methods sampling headspace (Larsen and Frisvad, 1995).

Selected Ion Flow Tube-Mass Spectrometry (SIFT-MS) provides rapid, broad-spectrum detection of trace VOCs in moderately complex gas mixtures. SIFT-MS quantifies VOCs to low part-per-billion (ppb) levels in whole air (i.e. without preconcentration) in real time (Senthilmohan et al., 2001). This technique has been used to study the VOCs produced by *Aspergillus*, *Candida*, *Mucor*, *Fusarium*, and *Cryptococcus* species (Scotter et al., 2005).

Proton transfer reaction-mass spectrometry (PTR-MS) ionizes organic molecules in the gas phase through their reaction with H_3O^+ , forming mostly MH^+ molecules (where M is a neutral organic molecule), which can then be detected by a standard quadrupole/multiplier mass analyzer (Lindinger and Jordan, 1998). PTR-MS can be used to quantify fungal VOCs since it has a fine detection capability and a fine scale time response (Ezra et al., 2004). Additionally, analyses can be run in real time without sample preparation, derivatization or concentration with the advantage of having sensitivities comparable to GC–MS. This technique has been used to quantify the VOCs of *Muscodor albus* (Ezra et al., 2004).

Booth et al. (2011) described a technique that rapidly traps and collects fungal VOCs that may have fuel potential. The trapping materials, Carbotrap A and B (Supelco) and bentonite-shale, were placed in a stainless steel column and the trapped fungal VOCs were recovered via controlled heating of the column followed by passage of the gases through a liquid nitrogen trap at a recovery rate of approximately 65–70 %. This method allows the recovery of mg quantities of compounds normally present in the gas phase that may be used for bioassays, further separation, and analyses (Booth et al., 2011), and potentially for nuclear magnetic resonance (NMR) spectroscopy to identify novel compounds produced by fungi.

The “Electronic nose”, or “E-nose”, is a promising new development in the detection of fungal volatile compounds. These instruments comprise arrays of electronic chemical sensors with appropriate pattern recognition systems, capable of recognizing simple or complex odors (Gardner and Bartlett, 1992; Wilson and Baietto, 2009). A typical E-nose system combines a multi-sensor array, an information processing unit, pattern recognition software, and a reference library (Wilson and Baietto, 2009, 2011). Sensing technology provides a qualitative assessment of the variations in mass, optical or electrical properties of the sensor material after exposure to volatile compounds. This technology yields “electronic fingerprints” that can be detected without the need to separate the

mixture into its components. Dedicated instrumentation has been developed for medical, military, pharmaceutical, and regulatory applications. For example, fungal VOC fingerprints can be used to noninvasively discriminate medically relevant fungi (Sahgal et al., 2006; Sahgal and Magan, 2008), and to determine the efficacy of and buildup of fungal resistance to anti-fungal drugs (Naraghi et al., 2010; Pont et al., 2012). In the food safety industry, this technology provides a means of early detection of mycotoxin-producing fungi in grains, fruit and meat products (Magan and Evans, 2000; Sahgal et al., 2007; Cabañes et al., 2009; Leggieri et al., 2010). Additionally, the E-nose shows promise in agricultural applications through determination of overall soil health in response to environmental factors or soil inputs (Bastos and Magan, 2007).

3. Early research on fungal volatiles and environmental health sciences

Microbial growth in damp indoor environments has been correlated with adverse impacts on human health. In particular, occupants of damp, moldy buildings, both residential and commercial, are at increased risks of respiratory symptoms, respiratory infections and exacerbation of asthma (IOM, 2004; WHO, 2009). In addition, symptoms related to occupancy in moldy buildings may include fatigue, headache, dermatological symptoms, gastrointestinal tract problems, reproductive effects as well as rheumatologic and other immune diseases (Apter et al., 1994; Redlich et al., 1997; Hodgson et al., 1998; Hodgson, 2000). The terms “mold related illness” or “sick building syndrome” commonly are used to describe this spectrum of ill-defined clinical conditions and complaints. Based on data from epidemiological studies and a limited number of laboratory toxicological studies, mostly on rodents, both the Institute of Medicine committee on *Damp Indoor Spaces and Health* (2004) and the World Health Organization committee on *Dampness and Mould* (2009) concluded that evidence from the published studies was insufficient to support a causal relationship between molds and most of the disease symptoms reported; however, evidence was sufficient to support an association between molds and upper respiratory tract symptoms, asthma symptoms in sensitized asthmatic persons, and hypersensitivity pneumonitis in susceptible persons. Moreover, there was suggestive evidence of association between molds and lower respiratory illness in otherwise healthy children (IOM, 2004; WHO, 2009). On the other hand, the postulated link between mold exposure and the less common human health effects is a controversial subject, fueled in part because many scientific studies have been conducted as part of the considerable litigation in the USA surrounding “sick building syndrome” (Apter et al., 1994).

The most intensive research on building related illness and “sick building syndrome” has focused on the possible role of mycotoxins, especially trichothecenes, as the etiological agents (Yang and Johanning, 1996; Robbins et al., 2000; Jarvis and Miller, 2005). Nevertheless, even high concentrations of spores and mycelial fragments rarely contain sufficient mycotoxins to induce the wide array of reported symptoms (Peraica et al., 1999; Straus, 2009). Mold VOCs have received less attention than mycotoxins, however a few groups have

hypothesized that they may be the etiological agents associated with “sick building syndrome” (Mølhave *et al.*, 1993; Mølhave, 2009). Indeed, exposure to VOCs from molds has been associated with symptoms including lethargy, headache, as well as irritation of the eyes and mucous membranes of the nose and throat. Respiratory tract symptoms include nasal congestion, sore throat, cough, phlegm production, and wheezing (Araki *et al.*, 2010).

When “indoor molds” such as species of *Aspergillus*, *Penicillium*, and *Stachybotrys* are grown on building materials under controlled laboratory conditions, complex and highly variable profiles of different VOCs can be generated that vary with species, substrate, length of incubation and other environmental parameters (Sunesson *et al.*, 1995; Claeson *et al.*, 2002; Claeson and Sunesson, 2005; Matysik *et al.*, 2008). When monitored outside of the laboratory, VOC profiles are even more changeable. The types and concentrations of VOCs in the indoor air of mold-infested buildings vary with the ventilation rate, moisture level, substrate, composition of mold population, area of the building/room, and other parameters (Morey *et al.*, 1997; Schleibinger *et al.*, 2008). Among the highest reported concentration for a single VOC found in problem buildings was for 1-octen-3-ol (900 $\mu\text{g}/\text{m}^3$ or 0.16 ppm) (Morey *et al.*, 1997).

The cytotoxicity of several microbial VOCs administered in fluid form directly into the culture media was evaluated in tissue culture assays, and concentrations of 1-octen-3-ol as low as 0.6 mM were found to be toxic (Kreja and Seidel, 2002a, b). Human volunteers exposed to 10 mg/m^3 of volatilized 1-octen-3-ol for 2 h reported minor irritation of eye, nose, and throat (Wälinder *et al.*, 2008). In our laboratory, we have shown that low concentrations of gas-phase 1-octen-3-ol are neurotoxic in a *Drosophila melanogaster* model (Inamdar *et al.*, 2010) as well as to human embryonic stem cells (Inamdar *et al.*, 2011). For a review of the toxicological potential of microbial VOCs see Korpi *et al.* (2009). Further research on the toxicological effects of fungal VOCs, especially 1-octen-3-ol, seems warranted.

4. Biocontrol and plant–microbe interactions

Volatiles are important in the functioning of both atmospheric (“above-ground”) and soil (“below-ground”) ecosystems. There is potential of fungal VOCs for biotechnological applications in agriculture, industry and medicine. In agriculture, the interest in fungal VOCs is for their potential as biological control (biocontrol) agents to control fungal pests to employ a more environmentally sound pest management strategy by reducing fungicide use on crop plants.

Belowground interactions

Soil fungistasis, the failure of fungal propagules to germinate or the inhibition of fungal hyphal growth under favorable temperature and moisture conditions (Watson and Ford, 1972), has been hypothesized to occur because of either competition for nutrients or release of inhibitory compounds in the soil. Recent data suggest a broader and more integrated theory of fungistasis, which includes the importance of

volatile compounds. For an excellent review on soil biostasis, see Garbeva *et al.* (2011). Fungistatic soils contained the VOCs, trimethylamine, 3-methyl-2-pentanone, dimethyl disulfide, methyl pyrazine, 2,5-dimethyl-pyrazine, *N*-dimethyloctylamine and nonadecane, while soils which showed no fungistasis did not (Xu *et al.*, 2004). These volatile compounds inhibited three fungal species, *Paecilomyces lilacinus*, *Pochonia chlamydospora*, and *Clonostachys rosea*, suggesting that the occurrence of volatile fungistasis may not need the direct competition between soil microorganisms, and may have a different mechanism than direct fungistasis (Xu *et al.*, 2004).

VOCs can permeate air-filled pores of soils and can travel long distances, depending on the properties of the habitat (Aochi and Farmer, 2005). This property may make fungal VOCs a useful addition to biocontrol strategies. For example, without any direct contact between the strains, the volatiles of wild-type antagonistic *Fusarium oxysporum* and its bacterial consortium inhibited the fungal growth of a plant pathogenic strain of *F. oxysporum* (Minerdi *et al.*, 2009). The VOCs of the endophyte *M. albus* also can be used to control soil-borne diseases. When *M. albus* was added to soil mixtures, it provided control of the pathogens *Rhizoctonia solani*, which causes damping-off of broccoli, and *Phytophthora capsici*, which causes root rot of bell pepper (Mercier and Manker, 2005). In addition to the inhibitory effects of certain VOCs on deleterious soil-borne organisms, stimulation or enhancement of soil-borne biocontrol agents may be another desired effect (Wheatley, 2002). When studied for their potential to be used together as biological control agents of plant pathogens, the volatiles emitted by *Trichoderma atroviride* increased the expression of a primary biocontrol gene of *Pseudomonas fluorescens* (Lutz *et al.*, 2004).

Fungal VOCs of soil-borne fungi may benefit plants by activating defense responses and priming them against future pathogen attack, as well as by providing growth promotion of nearby plants. Mixtures of bacterial VOCs can induce a defense response in plants (Ryu *et al.*, 2003). For example, when *Arabidopsis thaliana* was exposed to 1-octen-3-ol (“mushroom alcohol”), a major fungal VOC, the defense genes were up-regulated and provided protection from the attack of a pathogen, *Botrytis cinerea* (Kishimoto *et al.*, 2007). Exposure to allo-ocimene and a C-6 aldehyde activated similar defense responses in *A. thaliana* (Kishimoto *et al.*, 2006a, b). The VOCs of a strain of *F. oxysporum* (MSA 35) and its bacterial consortium, shown to be antagonistic to a pathogenic *F. oxysporum* strain, significantly enhanced the growth of lettuce (*Lactuca sativa*), with β -caryophyllene identified as one of the volatiles that generated the plant-growth promotion effect (Minerdi *et al.*, 2011).

On the other hand, fungal VOCs may negatively impact plant growth. Volatiles emitted by truffles (*Tuber* spp.) inhibited the growth of *A. thaliana* (Splivallo *et al.*, 2007a), which may be indicative of an ability of mycorrhizal fungi to create dead zones, potentially removing the competitors of their hosts (Splivallo *et al.*, 2011).

Aboveground interactions

As novel endophytic fungal species are isolated from tissues beneath the plant’s epidermal cell layers, researchers have

begun to identify and study their bioactive volatile metabolites. Endophytic fungi live within their hosts and cause no apparent harm (Bacon and White, 2000). They produce a mixture of numerous VOCs, and it is becoming apparent that the ecological role of these volatile compounds is far more complex than many researchers have previously appreciated. Furthermore, the VOCs of endophytic fungi may benefit the host plant by providing additional lines of defense against pathogens of their host plant (Macias-Rubalcava et al., 2010). For example, *M. albus*, produced VOCs that inhibit and kill plant pathogenic fungi and bacteria (Strobel et al., 2001). Additionally, the VOCs produced by *Muscodor yucatanensis*, *Muscodor fengyangensis*, and a second isolate of *M. albus* all inhibited pathogenic species of bacteria, fungi and oomycota (Atmosukarto et al., 2005; Macias-Rubalcava et al., 2010; Zhang et al., 2010). Lastly, cultures of *Muscodor crispans* produce a mixture of VOCs that inhibited a wide range of plant pathogens, including the fungi *Mycosphaerella fijiensis* (the black sigatoka pathogen of bananas), and the serious bacterial pathogen of citrus, *Xanthomonas axonopodis* pv. *citri* (Mitchell et al., 2010).

The VOC profiles of the *Muscodor* species included esters, alcohols, acids, lipids and ketones (Strobel et al., 2001), while a *Phomopsis* sp. produced a unique mixture of VOCs including sabinene (a monoterpene with a peppery odor) only previously known from higher plants. Some of the other more abundant VOCs recorded by GC/MS from the *Phomopsis* sp. were 1-butanol, 3-methyl-, benzeneethanol; 1-propanol, 2-methyl and 2-propanone (Singh et al., 2011). Mixtures of commercially available compounds, such as bulnesene, valencene, and synthesized compounds, such as propanoic acid, 2-methyl-, 3-methylbutyl ester, and 1-butanol, 3-methyl-, acetate were tested against the pathogens and yielded similar inhibitory effects to the *M. albus*-produced VOCs (Strobel et al., 2001). Nevertheless, when that mixture of VOCs was broken down into several classes of compounds, the same inhibitory effects were not achieved, suggesting that it is the suite of VOCs that contributes to the antifungal activity (Strobel et al., 2001).

Along with providing defenses against pathogens of their host, certain endophytic fungi may aid in the plant's survival in certain habitats. A *Phoma* sp. isolated from creosote bush emits VOCs that may contribute to the ability of this shrub to survive harsh desert habitats (Strobel et al., 2011). This *Phoma* sp. produces a unique mixture of VOCs, including trans-caryophyllene, a series of sesquiterpenoids, some alcohols and several reduced naphthalene derivatives. These VOCs inhibited or killed a range of plant pathogens, including *Verticillium*, *Ceratocystis*, *Cercospora* and *Sclerotinia*, while *Trichoderma*, *Colletotrichum* and *Aspergillus* were not greatly affected (Strobel et al., 2011).

Additionally, fungal VOCs may contribute to or may enable their host plant to outcompete neighboring plants. For example, the VOCs produced by *M. yucatanensis* were toxic to the roots and inhibited seed germination of amaranth, tomato and barnyard grass (Macias-Rubalcava et al., 2010). The VOCs were also toxic to other endophytic fungi, possibly enhancing growth of their host plants, and potentially minimizing the nutrients the plant provides to its endophytes (Macias-Rubalcava et al., 2010).

5. Mycofumigation and other antibiotic effects

The VOCs of *M. albus* are useful for the control of post-harvest plant diseases, in what has been termed "mycofumigation" (Stinson et al., 2003). In *in vitro* experiments, the VOCs of *M. albus* were toxic to the peach pathogens, *Penicillium expansum*, *B. cinerea* and *Monilinia fructicola*, furthermore, the volatiles prevented fungal contamination of post-harvest peaches over 7 d of storage (Mercier and Jiménez, 2004). *M. albus* volatiles also could be used for non-agricultural biofumigation and were investigated for their potential to control building molds. *M. albus* VOCs significantly reduced growth of common building fungi (Mercier and Jiménez, 2007). Additionally, the VOCs of *Oxyporus latemarginatus* EF069, an endophyte isolated from red peppers, inhibited the mycelial growth of several plant pathogens known to damage post-harvest fruit (Lee et al., 2009). *O. latemarginatus* EF069 could be used in mycofumigation as the VOCs reduced post-harvest decay of apples caused by *B. cinerea* and *Rhizoctonia* root rot of moth orchid (Lee et al., 2009).

The antibiotic effects of fungal VOCs eventually may provide an addition to the arsenal of antibiotics used in managing human disease, though this remains to be seen in the future. Indeed, the VOCs of *M. crispans* killed several human pathogens, including *Yersinia pestis*, *Mycobacterium tuberculosis* and *Staphylococcus aureus*. *M. crispans* produces the VOC propanoic acid, 2-methyl-, 3-methylbutyl ester, which when tested alone was also inhibitory to a number of human pathogens, including three drug-resistant strains of *M. tuberculosis* (Mitchell et al., 2010). Another endophyte, *M. fengyangensis*, killed the pathogen *Escherichia coli* (Zhang et al., 2010).

6. Semiochemicals: VOCs and arthropods

Fungal volatiles can serve as signaling molecules ("infochemicals" or "semiochemicals") that affect organisms within a species, among species, and across kingdoms. Entomologists have discovered that fungal VOCs have properties as pheromones, allomones, kairomones etc. (Rohlfes et al., 2005; Mburu et al., 2011). A few examples are given below.

Emission of VOCs by fungi may be an efficient way of defending against fungal feeders. For example, 1-octen-3-ol produced by the mushroom *Clitopilus prunulus* deterred banana slugs (*Ariolimax columbianus*) from consuming the mushrooms (Wood et al., 2001). On the other hand, some fungal VOCs provide location cues for host selection in fungivorous arthropods (Hedlund et al., 1995). 1-octen-3-ol produced by the wood-rotting white rot fungus *Trametes gibbosa* serves as an attractant for fungus-eating beetles (Coleoptera) (Thakeow et al., 2008). Another species of white rot, *Trametes versicolor*, produced sesquiterpenes such as δ -cadinene, followed by β -guaiane, isodene and γ -patchoulene, that attracted fungivorous beetles in behavioral experiments (Drilling and Dettner, 2009). An interesting side note: an earlier study found that after degradation of European Beech (*Fagus sylvatica*) lignin and cell structures by *T. versicolor*, sesquiterpenes were the only volatiles produced (Holighaus and Schütz, 2006).

Fungal VOCs also function to attract insects to other food sources. For example, 1-octen-3-ol when emanated from human skin serves as a host odor cue that attracts blood-sucking insects, such as the mosquito *Anopheles gambiae* (Kline et al., 2007). Additionally, fungi can produce pseudo-flowers that mimic real flowers in sight and smell by producing volatile compounds that are used in pollinator attraction to facilitate pollen transfer (Ngugi and Scherm, 2006). In the *Puccinia monoica*-crucifer pathosystem, these scents are made up primarily of aromatic alcohols, aldehydes, and esters (Raguso and Roy, 1998). The most abundant volatiles in *Puccinia arrhenatheri*-infected *Berberis vulgaris* include indole, methyl nicotinate, α -phellandrene, carvacryl methyl ether, and jasmine lactone (Naef et al., 2002). Additionally, *Botanophila* flies act as gamete vectors for the endophytic fungal genus *Epichloë*, commonly found in pooid grasses, and are attracted by a volatile sesquiterpenoid alcohol named chokol K (Schiestl et al., 2006), and a methyl ester, methyl (Z)-3-methyldodec-2-enoate (Steinebrunner et al., 2008), both emitted by the fungus. In addition to attracting 'pollinators', bioassays have shown that chokol K can reduce the spore germination and growth of mycoparasitic fungi at ecologically relevant concentrations (0.014, 0.023 and 0.045 mM), indicating the putative defensive role of VOCs produced by epiphytic fungi (Steinebrunner et al., 2008).

Fungal VOCs also are being investigated for their insecticidal activity. For example, the VOCs produced by *Muscodor* spp., including nitrosoamide, have been shown to kill insects (Strobel et al., 2010). *Muscodor vitigenus* produces naphthalene, formerly used in "mothballs", and functions as an effective insect repellent (Daisy et al., 2002). In addition, VOC profiles have been correlated with varying levels of pathogenicity of entomopathogenic fungi, *Beauveria bassiana* and *Metarhizium anisopliae*, studied for their potential as biocontrol agents to reduce termite populations (Hussain et al., 2010). The volatile profile of the virulent inocula contained n-tetradecane and alkenes, while the non-virulent strains contained many branched alkanes (Hussain et al., 2010).

7. Potential biotechnological applications of fungal VOCs

The search for new plant and microbial species in hopes of finding novel biotechnological products is termed "bio-prospecting". Most of this search has focused on the discovery of secondary metabolites of potential pharmacological, industrial or other commercial value, especially from soil microorganisms. Moreover, there are 300,000 species of vascular plants, most of which are likely to be harboring hitherto undescribed endophytes (Bacon and White, 2000). These fungal endophytes may produce a wealth of novel bioactive metabolites that have yet to be discovered. The endophytic species that we discussed above were discovered via bio-prospecting, leading to the identification and study of some interesting new bioactive metabolites and VOCs with biofuel potential.

It is likely that many hitherto overlooked and undiscovered VOCs with biotechnological potential remain to be developed. Biocontrol strategies are a case in point. For example,

Trichoderma spp. have been used as biological control agents since the 1930s (Howell, 2003), and many field experiments have demonstrated that applications of *Trichoderma* spp. promotes the growth of plants and limits the growth of plant pathogens (Altomare et al., 1999). *Trichoderma* spp. are effective biofungicides, enzymatically degrading other fungi, producing anti-microbial compounds that kill pathogenic fungi, and out-competing pathogenic fungi for space and nutrients (Verma et al., 2007; Vinale et al., 2008). Additionally, *Trichoderma* spp. may induce systemic resistance, priming plants for pathogen attack and allowing them to protect themselves, as do other soil-dwelling microbes, such as rhizobacteria (Van Wees et al., 2008). Work in our laboratory has shown that *A. thaliana* seedlings, grown in the presence of fungal VOCs without physical contact between the plants and the fungus, showed increased biomass and chlorophyll concentration (Hung et al., in press). Because *Trichoderma* species are known to produce numerous VOCs (Wheatley et al., 1997; Stoppacher et al., 2010), and because other VOC-producing soil organisms benefit plants (Van Loon et al., 1998), further studies on the benefits of *Trichoderma*-produced VOCs are warranted.

Most of the research on fungi and biofuel has focused on finding efficient enzymes for degrading biomass into fermentable substrates. In addition, fungal VOCs may have implications for utilization of biologically based energy sources by converting plant waste directly into diesel (Strobel et al., 2011). VOC production by *Ascocoryne sarcoides*, *Ascocoryne cylichium* and *Ascocoryne solitaria*, saprophytes isolated from deadwood, generated VOC profiles including alkanes, alkenes, alcohols, ester, ketones, acids, benzene derivatives and terpenes, some of which are similar to biofuel target molecules (Griffin et al., 2010). Further, many of the *Ascocoryne* strains produced sesquiterpenes (Griffin et al., 2010), which are a potential source of diesel or jet fuel alternatives due to their cyclic and branched nature (Rude and Schirmer, 2009). The monoterpene 1,8-cineole, an octane derivative, also has potential use as a fuel additive, as do the other VOCs produced by *Hypoxylon* sp. (Tomsheck et al., 2010). In addition to alkanes and long-chain HCs, many fungal species produce other potential biofuel targets, such as ethylene, ethane, propane and propylene (Ladygina et al., 2006). Some fungi also produce terpenes and isoprenoids, another diverse family of compounds that may be used as fuels (Grigoriev et al., 2011). In summary, fungi are an excellent platform for exploiting biosynthetic routes to hydrocarbon biofuels or biofuel precursors (Grigoriev et al., 2011).

It is likely that fungal VOCs are a chemical class with potential biotechnological applications with greater market value beyond those in the food or agricultural industries. Available studies have only scratched the surface. Nevertheless, road-blocks remain before their biotechnological potential can be exploited. Fungal VOCs are produced in small quantities, making them difficult to characterize and study. Little is known about their biosynthesis, although genomic, transcriptomic and metabolomic studies are beginning to correlate gene expression to volatile production (Gianoulis et al., 2012). Ultimately, by using genetically modified fungi with impaired volatile formation, the suite of volatiles that fungi produce under different culture conditions will be determined. This is an essential step in linking genes to compounds and to

defining the biosynthetic pathways that lead to the production of important compounds. Because fungal VOCs cannot be used directly as a fuel source, understanding these genetic pathways is paramount. With this knowledge, the necessary genes can be overexpressed in producing species or transferred to industrially tractable heterologous hosts for the large-scale production of compounds of human interest.

For most of the 20th century, fungal bioprospecting has focused on the search for traditional secondary metabolites with drug value (e.g. penicillin, lovastatin) or for enzymes with new applications (e.g. biomass degrading enzymes from thermophiles). A concerted search for new biotechnological products among VOCs will require a paradigm shift in the scientific community.

Volatiles represent a new frontier in bioprospecting. When coupled with the power of “omics” technologies, the study of these gas-phase compounds promise the discovery of new products for human exploitation and will generate new hypotheses in fundamental biology.

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