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Fungal Volatile Organic Compounds: More Than Just a Funky Smell?

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Abstract

Many volatile organic compounds (VOCs) associated with industry cause adverse health effects, but less is known about the physiological effects of biologically produced volatiles. This review focuses on the VOCs emitted by fungi, which often have characteristic moldy or "mushroomy" odors. One of the most common fungal VOCs, 1-octen-3-ol, is a semiochemical for many arthropod species and also serves as a developmental hormone for several fungal groups. Other fungal VOCs are flavor components of foods and spirits or are assayed in indirect methods for detecting the presence of mold in stored agricultural produce and water-damaged buildings. Fungal VOCs function as antibiotics as well as defense and plant-growth-promoting agents and have been implicated in a controversial medical condition known as sick building syndrome. In this review, we draw attention to the ubiquity, diversity, and toxicological significance of fungal VOCs as well as some of their ecological roles.

Contents

INTRODUCTION

Volatile organic compounds (VOCs) are carbon-containing compounds of low molecular mass that easily evaporate at normal temperatures and pressures (37). There is a large toxicological literature on anthropogenic volatiles, but less is known about the physiological and pathological aspects of biogenic VOCs. This review focuses on the VOCs produced by fungi, excluding CO_2.

Most microbial VOCs have characteristic odors (107). Some of them have pleasant associations for humans as components of wine, beer, and fermented foods. Conversely, others are associated with rotten foods, dirty socks, sewerage facilities, water-damaged buildings, waste sites, and decay. More than 300 VOCs from microscopic and macroscopic fungi have been described. Any species of fungus may simultaneously emit dozens of different volatiles as mixtures of alcohols, ketones, esters, small alkenes, thiols, monoterpenes, and sesquiterpenes (65). It is common for the same chemical species of VOC to be produced by dozens, if not hundreds, of fungal species. For example, 1-octen-3-ol, a breakdown product of linoleic acid, also known as mushroom alcohol, is nearly ubiquitous among both mushrooms and molds (23). Geosmin, a major odor constituent in soils, is produced by many streptomycetes and cyanobacteria in addition to fungi (106, 107). Few, if any, fungal VOCs are uniquely associated with fungal metabolism. A useful compendium of fungal VOC structures and species of origin, based on papers published between 1936 and 2005, was published in French by Chiron & Michelot (20). A database of thousands of microbial volatiles including those from both bacteria and fungi is available online (73).

The proportion and concentration of each VOC vary depending on the substrate, moisture level, ambient temperature, duration of fungal growth, and interactions with other organisms. In addition to compounds produced by fungal biosynthetic pathways, complex volatile cocktails include nonspecific biotransformation and degradation products of substrates that have been broken down by fungal extracellular enzymes. The way in which VOCs are collected also affects the volatile profile reported (43, 70). In order to describe this dynamic and complicated metabolic mixture, some researchers use the term volatome or volatilome, defined as the total complement of compounds produced by a given organism at a given time (36, 79). Volatomes/volatilomes are a subset of metabolomes whereby biologists take a snapshot of the entire metabolic profile of an organism or system (102). Metabolomes, unlike genomes, change dynamically with physiological status, environmental parameters, and so forth.

The literature on fungal VOCs is scattered within different disciplines, such as aroma and flavor chemistry, building science, chemical ecology, industrial hygiene, medical mycology, and plant pathology. Here, we attempt to bring together examples from this disparate and enormous literature with emphasis on the functional and possible toxicological effects of fungal VOCs.

CHEMICAL CHARACTERIZATION

Isolation and Identification

The quantification and identification of biogenic VOCs pose many technical challenges. By definition, these compounds are highly evaporative, and VOC loss can occur easily during sample handling and assay procedures (32). In addition, volatiles tend to be produced in low concentrations in complex mixtures. No single method for collection, identification, and quantification of VOCs is optimal, and the best method will depend on the compounds of interest, the intended application, the required sensitivity, the cost, and the ease of use. In classical work, the extraction, separation, and identification steps were separate. Many early studies on fungal VOCs used steam distillation under nitrogen, followed by liquid extraction and concentration (55, 108). Current methods usually use gas chromatography (GC) combined with a mass spectrometer (GC-MS) for separation and identification of compounds (130). The headspace gas above a sample can be collected with a gas-tight syringe and injected directly into a gas chromatograph. Alternatively, volatiles can be absorbed onto various polymers such as Texas GC or Chromosorb 102 and released though extraction with organic solvents or through thermal desorption (105). Solid phase microextraction (SPME) is a portable method whereby VOCs are concentrated on a fiber and transported to the detector and desorption occurs in the GC injector itself (50). SPME is useful for taking environmental samples that are later transported back to the laboratory. Zhang & Li (128) have provided a useful overview of analytical methods for VOCs.

Finally, the so-called artificial nose or electronic nose combines a multisensory array, an information-processing unit, pattern recognition software, and reference library databases (122). The resultant electronic fingerprints are unique aroma signatures that promise to detect odor profiles without requiring the mixture to be separated into its components. Dedicated instrumentation has been developed for military, pharmaceutical, and regulatory applications, and this technique may have utility in indoor environments (69).

Classification, Biosynthesis, and Challenges

The chemical nomenclature surrounding VOCs is employed somewhat irregularly. The International Union of Pure and Applied Chemistry (IUPAC) conventions are encountered in most scholarly publications. Nevertheless, common names and synonymy are rampant and can confuse the unwary reader. This is particularly true of compounds that are sold for commercial purposes. For example, 2-buten-1-ol is a commercial solvent that also is produced by filamentous fungi, and it functions to change aflatoxin production and conidiation in *Aspergillus parasiticus* (99). Synonyms include 2-butene-1-ol, 2-butenol, 2-butenyl alcohol, 3-methylallyl alcohol, crotonyl alcohol, crotyl alcohol, (2E)-but-2-en-1-ol, and *trans*-crotonyl alcohol. A useful table of synonymy for fungal VOCs was collated by Korpi et al. (63). Recently, the Lemfack group has developed a database of microbial VOCs (mVOCs) that is freely available at the website **http://bioinformatics.charite.de/mvoc**. The database provides information about chemical structures, mass spectra, producing organisms, and the role of individual VOCs in specific metabolic or signaling pathways (73).

Several systems are used to classify VOCs into structurally similar groups. In general, a relatively small number of skeletal motifs are multiplied into a large range of derivatives, positional isomers, and stereochemical variants. In some schemes, compounds are organized by the size of their carbon skeleton into C-6 compounds, C-8 compounds, and so forth. In other schemes, compounds are categorized as plain hydrocarbons, heterocyclic compounds, thiols, alcohols, phenols, acids, and isoprenoids and their respective derivatives. Chirality also is important, and stereoisomers may have distinctly different odors. In a famous example from plants, *R*-(−)-carvone smells like spearmint while its mirror image, or enantiomer, *S*-(+)-carvone smells like caraway (100). In fungi, the R form of 1-octen-3-ol is more mushroom-like in odor; the S form is grassier and moldier (84). Odor thresholds, which tend to be extremely low for many biologically generated VOCs, are often different for enantiomers.

Some authors call VOCs collectively secondary metabolites, but since most of them are degradation products of fatty acids, simple biotransformation products of amino acids, or merely incidental breakdown products of fungal extracellular enzymes acting on exogenous substrates, we avoid this usage. Secondary metabolites are biosynthesized by multi-enzyme complexes whose genes are closely linked, creating distinctive bioinformatics signatures in genome data (57, 58). Less is known about the pathways that fungi use to produce VOCs. In early work, the biosynthetic pathways for geosmin (11) and 1-octen-3-ol (7) were elucidated. It is probable that volatile thiols are amino acid derived (114). Nonetheless, the metabolic origin of most VOCs has not been studied. Given the relative shortage of information about the enzymes and pathways involved in VOC production, it is difficult to exploit emerging genomic resources.

FUNGAL VOLATILES IN HUMAN FLAVOR AND TASTE

Volatiles comprise the aroma component of flavors and are ubiquitous in foods and drinks (78, 90). Many synthetic versions of natural volatiles, available in liquid form, are used as flavor-enhancing agents in modern food processing as well as pharmaceutical and cosmetic formulations. Dunkel et al. (27) have compiled a general database of flavors and scents. Both the US and European legislatures have defined the term "natural flavors" as compounds obtained from living cells, which include food-grade microbes and their enzymes. Many high-demand volatile flavor compounds are produced in low quantities in plants but can be generated de novo by filamentous fungi. Therefore, as consumer demand for natural flavoring ingredients has grown, food technologists have often utilized fungal fermentation processes for manufacturing desirable plant VOCs (1). For example, some strains of the common soil fungus *Trichoderma* emit 6-pentyl-α-pyrone (also known as 6-n-pentyl-2H-pyran-2-one; IUPAC = 6-pentylpyran-2-one). This fungal product has a distinct coconut odor and is a widely employed natural ingredient (51). Basidiomycetes are particularly useful in generating aroma compounds (75). For example, *Nidularia* makes 4-(4-hydroxyphenyl)-butan-2-one (raspberry ketone), one of the distinctive components of raspberry flavor (13). Microbial species associated with the aroma and flavor industry have been reviewed elsewhere (2, 76).

Yeasts contribute to the aromas of wines, beers, and myriad other products that they ferment. It would require several reviews to do justice to this topic, so it will not be covered further here except to mention that one of the more user-friendly and popular classification systems ever developed for smells was created by Ann C. Noble, Department of Viniculture at the University of California, Davis, and is called the Wine Aroma Wheel (**http://winearomawheel.com/**). The Wine Aroma Wheel provides standardized terminology, and this framework has been widely adapted and copied for categorizing smells beyond wine. A readable summary of other aroma wheels (e.g., beer, cheese, and chocolate), as well as a brief history of scientific smell classification systems dating back to Linnaeus, is given in *What the Nose Knows: The Science of Scent in Everyday Life* (33).

The dominant aroma associated with mushrooms is due to a mixture of aliphatic, oxygenated, 8-carbon compounds, especially 1-octen-3-ol but also including 1-octen-3-one, 3-octanol, 3-octanone, and others. The odor of these compounds is customarily described as mushroom-like or mushroom-like/buttery (22, 80). Each mushroom species has a characteristic mixture of other volatile flavor components that may include additional aliphatic, terpenoid, aromatic, and sulfur-containing compounds (119). For example, shiitake mushroom (*Lentinula edodes*) produces several thiols similar to those found in garlic and onions (111).

Truffles emit the most famous of the fungal odor bouquets. Scientists have isolated hundreds of VOCs from truffle fruiting bodies; it is likely that at least some of these VOCs actually are metabolic products of bacteria and yeasts that live in close association with the subterranean fungus (113). These gourmet macrofungi live in mycorrhizal associations with trees. Because they grow underground and are difficult to find, they are hunted by pigs or dogs trained to detect their smell. With beguiling aromas, and purported to be aphrodisiacs, truffles sell for high prices to food connoisseurs. They are the subject of an enormous folklore (41, 96, 97). Splendid descriptions of the intoxicating odor of truffles, and various human reactions to this odor, are given in *Mycophilia: Revelations from the Weird World of Mushrooms* (17).

Several traditional Asian food fermentations utilize filamentous fungi. Koji is an abbreviation of the Japanese word *kabi-tachi*, which means "bloom of mold" and refers to a mixture of rice or soybeans infiltrated with the hyphae of growing *Aspergillus oryzae* or *Aspergillus sojae*. As the mold grows and secretes extracellular enzymes, the koji becomes an aromatic combination of partially degraded substrate, mold mycelia, and a variety of volatile and nonvolatile mold metabolites. Koji fermentations are central to the preparation of shoyu (soy sauce), miso (fermented soybean paste), and sake (rice wine). The flavors and smells of these venerable Asian fermentations depend largely on the VOCs produced by mold metabolism. The specific odor bouquets vary with the substrates employed, strains of fungi, secondary fermentations, and so forth (60, 115).

FUNGAL VOCs AS INDIRECT MONITORS OF MOLD GROWTH

Quantifying filamentous fungal growth is a difficult challenge. Counting colony-forming units, direct microscopy, and determination of ergosterol are commonly used classical methods (89). For analysis of fungal growth in built environments, bulk lift and wipe sampling of surfaces may be combined with various air filtration sampling techniques. Because moldy odors often are detected even in the absence of visible fungal growth, fungal VOCs can serve as indirect indicators. The mammalian olfactory system is an excellent detection system. The human nose has long been used to detect the presence of molds associated with food spoilage, decaying paper, damp cellars, and the like. Among the major volatiles contributing to mold odors described as musty or sour are E-methyl-1-propanol, 3-methyl-1-butanol, 1-octen-3-ol, 3-octanone, 3-methylfuran, ethyl acetate, 2-methyl-isoborneal, and geosmin (105). Dogs, which have exquisite olfactory capacity, can be trained to detect mold odors (56). In recent years, both human and canine noses have been supplemented with various electronic nose technologies. For example, the plant pathogen *Tilletia caries*, or common bunt, produces a fish-like odor, mostly associated with trimethylamine, which is problematic in cereal products. An electronic volatile compound mapper was as effective as a human sensory panel in separating *Tilletia*-infested wheat from noninfested samples (18).

Agriculture

The off odors of molds have been used as indicators of food and feed spoilage in locations that are inaccessible to direct sampling techniques (105). A list of VOCs detected in relation to *Aspergillus*-, *Fusarium*-, and *Penicillium*-related spoilage of agricultural commodities has been compiled by Jelen & Wasowicz (54). VOCs also have been used both to detect mycotoxigenic fungi and to inhibit the production of mycotoxins. Aflatoxigenic *Aspergillus flavus* produced several compounds (α-gurjunene, *trans*-caryophyllene, and cadinene) that were not detected from nontoxigenic strains (127). Volatile terpenes were correlated in the same way with the formation of trichothecene mycotoxins from *Fusarium* species (52, 53). Volatile compounds produced by both *Aspergillus nidulans* and *A. parasiticus* affect aflatoxin biosynthesis. Specifically, 2-ethyl-1-hexanol inhibited growth and increased aflatoxin accumulation in *A. parasiticus*, while 2-buten-1-ol (crotyl alcohol) exerted dose-dependent upregulatory and downregulatory effects on aflatoxin production (98). Similarly, ethylene, a well-known biologically active volatile, inhibited aflatoxin production in a dose-dependent manner (99).

Built Environments

Built environments harbor complex microbial communities (86). When moldy odors are detected indoors, they are a sign that mold growth is present behind walls or in ducts, even when none is readily apparent on indoor surfaces. In general, the concentrations of fungal VOCs are extremely low, often only near 1 $\mu g/m^3$, but given the sensitivity of the human olfactory system, these smells are good indicators that hidden mold growth is present (40, 71, 104). Some workers have grown indoor molds in the laboratory and observed resultant VOC profiles in order to discover reliable measures for using VOCs to detect fungal contamination (101). To date, however, no single VOC has emerged as a reliable indicator of mold growth on building materials (65), although certain compounds are observed more often than others. These include 1-octen-3-ol, 3-octanol, 2-nonanone, 2-methyl-1-propanol, dimethyl sulfide, 3-methyl-2-butanol, 2-pentanone, 2-hexanone, and thujopsene (28, 63, 130).

Biomedical Applications

Since at least the time of Hippocrates, odors emanating from sick people have been used to diagnose specific diseases. VOCs originate from blood, breath, feces, sputum, sweat, urine, or vaginal secretions and yield distinguishing odor signatures for several cancers, genetic conditions, and infectious diseases, including invasive aspergillosis (25, 79, 110). For fungal pathogens, the greatest focus has been on *Aspergillus fumigatus*, a filamentous species that is the main causative agent of invasive aspergillosis, a potentially lethal systemic disease in immunocompromised patients (36). The compound 2-pentylfuran, not normally produced by mammalian metabolism, has been detected in the breath of patients infected with *A. fumigatus* (19). Unfortunately, a number of foodstuffs, including soy milk, Marmite vegetable extract, and peanuts, also contain 2-pentylfuran, which may confound the tests (14). Distinctive volatile profiles also have been observed for several species of *Candida*, including *C. albicans*, *C. glabrata*, and *C. tropicalis* (94). When human lung cells were cultured in vitro and inoculated with *A. fumigatus*, no 2-pentylfuran was found, but several sesquiterpenes including farnesene and bisabolene were identified (9). The difficulty of making a diagnosis of invasive aspergillosis in time to allow effective treatment makes the use of VOC markers for preliminary identification extremely attractive (36, 62). It is hoped that eventually VOCs may provide noninvasive diagnostic signatures for a variety of difficult-to-diagnose fungal diseases (34).

PHYSIOLOGICAL EFFECTS OF FUNGAL VOCs

Studies on the natural physiological effects of VOCs pose particular challenges. As organisms grow, mature, deplete substrates, and interact with one another, their VOC profiles change.

Therefore, when observing the responses of one organism to the VOCs emitted by another, it is difficult to determine which component(s) of a VOC blend is causing a particular functional response. In many cases, it requires a combination of several VOCs to elicit a certain physiological effect. Further, organisms may be participating in reciprocal cross talk using volatile signaling. Another complication is that controlled experiments are conducted in contained microcosms such as growth chambers, incubators, and other vessels. These microcosms are necessary to contain the VOCs and collect headspace but inevitably change the ratio of O_2 and CO_2, as well as the ratio within the component volatile mix, as compared to a ventilated atmosphere.

In biological systems, volatile-mediated communication occurs at the individual, interorganism, and interspecific levels. VOCs can easily disperse through the air and soil, so they are effective infochemicals across nonaqueous environments. Moreover, many of them are lipophilic, so they work well in signal-receptor systems. VOCs emitted by green plants play essential roles in pollination, seed dispersal, defense against herbivory, and resistance to plant pathogens (15, 37, 95). There has been a growing number of reports suggesting that microbial and fungal VOCs are actively involved in constructive microbe-plant interactions to support plant health (15, 16, 72, 74). In addition, some fungal VOCs act as antimicrobial agents and antibiotics (116, 117), in insect attraction and repulsion (31), as signals for fungal development (95), and/or as postulated contributors to adverse human health (49, 86, 123). Chemical ecologists who study plant volatiles have developed a theoretical framework that can guide cognate research for emerging studies on fungal VOCs.

Antibiosis and Mycofumigation

Some of the most exciting developments concerning fungal VOCs come from the study of endophytes, species that colonize living internal plant tissues without causing any overt negative effects (8). Bacterial and fungal endophytes constitute the plant microbiome. One VOC-emitting, nonsporulating, filamentous fungal species originally isolated as an endophyte of the spice tree *Cinnamomum zeylanicum* emitted VOCs that killed bacteria and fungi. It was named *Muscodor albus*, for "stinky white" fungus. At least 28 VOCs were identified from laboratory cultures of *M. albus*, encompassing acids, alcohols, esters, ketones, and lipids (116). Application of the antimicrobial properties of this VOC cocktail to control microbial contamination has been termed mycofumigation (117). Mycofumigation by *M. albus* has been applied to control smut-infected crops (82) as well as molds growing on drywall in buildings (81). The mode of action of the VOCs active in *M. albus* mycofumigation has been determined using genetic screens in *Escherichia coli*; the toxigenic effects were associated with disruption of the cell membrane and DNA damage (5). Independently of the discovery of the antibiotic effects of *M. albus* volatiles, other groups have reported on the similar toxigenic effects of fungal volatiles. For example, in one early study, *Trichoderma* sp. was shown to make antibiotic volatiles (26). Subsequently, the antimicrobial effects of *Trichoderma* VOCs have been observed many times and exploited to control plant-pathogenic species (66). Another phenomenon that has been observed for centuries is that truffles sometimes can be detected by patches of dead or sickly vegetation under the trees on which they are mycorrhizal (92). Splivallo et al. (112) showed that volatiles emitted by truffles can inhibit plant growth.

When volatiles were extracted from the oyster mushroom, *Pleurotus ostreatus*, the major compounds isolated were 3-octanone, 3-octanol, 1-octen-3-ol, 1-octanol, and benzaldehyde. With the exception of benzaldehyde, each of these compounds inhibited the growth of *Bacillus cereus*, *Bacillus subtilis*, *E. coli*, and *Salmonella enterica* Typhi at the concentrations found in the mushroom fruit body. Mixtures of the compounds completely inhibited the growth of all the bacteria tested (10).

Plant pathologists have long noticed the fungistatic and fungicidal effects of wound volatiles, compounds produced by plants in response to certain biological and mechanical injuries. Many of these plant volatiles have both aroma and functional characteristics; i.e., they smell and are fungistatic or fungicidal or have roles in attracting insect predators. In particular, C_6 aldehyde lipoxygenase-lyase pathway products such as hexanol, 1-hexanol, (E)-2-hexen-1-ol, and others have been tested as postharvest fumigants for control of *Botrytis cinerea*, *Penicillium expansum*, and other fungi that cause rots of berries and fruits (6, 88).

Fungal VOCs as Semiochemicals

Chemical ecologists have uncovered numerous chemical signaling mechanisms that control plant-arthropod interactions and introduced the word "semiochemical" to describe a large group of signaling molecules that encompass attractants, repellents, allomones, kairomones (host location cues), and pheromones (mate location signals) in arthropods (24, 43). For example, the volatiles 1-octen-3-ol, butanone, 3-methyl-2-hexenoic acid, and 7-octenoic acid all function as host location cues (77). Because the structural diversity of VOCs is somewhat constrained, the behavioral response of insects often depends on the detection of more than one component of a volatile blend (39). In some cases, mosquitoes, midges, flies, and other arthropod pests can be monitored and controlled by appropriate manipulation of mixed semiochemicals (3).

The volatile constituents of fungi are important in interspecific signaling. Many fungi depend on insects for spore dispersal. For sexual reproduction to occur in *Epichloë*, an endophytic clavicipitacean fungus that infects grasses, opposite mating types must come in close contact. Fungal stromata specifically attract female flies of the genus *Botanophila* that oviposit on the fungus and in the process facilitate the cross fertilization. Fly larvae depend on the fertilized stroma as a food source; the fungi need the flies for reproduction; the grass host, in turn, benefits from secondary metabolites produced by the endophyte that provide increased resistance to herbivores. The sesquiterpene alcohol chokol K, a fungal VOC with known fungitoxic activity, has been identified as the insect attractant (103). Numerous other examples could be cited. In summary, entomologists and chemical ecologists form scientific communities that make an outsized contribution to our overall understanding of the functionality of fungal VOCs.

Oxylipins and the 1-Octen-3-ol Family

Oxylipin is a term used to describe collectively a group of oxygenated fatty acids and the metabolites derived from them. Oxylipins are crucial for overall plant growth and provide a defensive mechanism against pathogen infection, insects, and wounding (109). Eight-carbon alcohols, aldehydes, and ketones are especially characteristic of fungal volatile metabolism and are multifunctional in nature. Of these, 1-octen-3-ol, sometimes known as mushroom alcohol or matsutake alcohol, is probably the single most common metabolite found in fungal VOC profiles. It is formed by the oxidative breakdown of linoleic acid, is a component of many essential oils distilled from plants, and is especially characteristic of mushrooms and molds (20, 23, 43, 124). It can be produced in a bioreactor by *Agaricus bisporus* (83).

1-Octen-3-ol has many reported functions, which include regulation of plant development and fungal spore inhibition. It inhibits mycelial growth of *Penicillium expansum* at low (1.25 mM) concentrations (91) and also performs a role of an autoinhibitor of spore germination in *Penicillium paneum* (21). In *Trichoderma*, low concentrations of 1-octen-3-ol, 3-octanol, and 3-octanone lead to conidiation, while both conidiation and growth are inhibited at higher concentrations of 1-octen-3-ol (0.5 mM) and 3-octanol and 3-octanone (both 1 mM) (87). Developmental regulation of aspergilli is often mediated by oxylipins (118). When *Arabidopsis thaliana* seeds were exposed to vapors of enantiomers of 1-octen-3-ol (R and S), a dose-dependent retardation of seedling formation occurred with all tested levels of both enantiomers (42). In another study of 23 fungal VOCs tested individually on *A. thaliana*, 4 (1-octen-3-one, 2-ethylhexanal, 3-methylbutanal, and butanal) completely inhibited germination after 72 h of exposure (44). In *Arabidopsis*, both 1-octen-3-ol and *trans*-2-octenal cause bleaching and an increase in levels of reactive oxygen species in exposed plants (112). Similarly, upon exposure of 1-octen-3-ol to *Arabidopsis*, there is upregulation of the defensive genes, which in turn supports the protection from the pathogen *B. cinerea* (59). Vapors of 1-octen-3-ol reduce the incidence of bubble disease in *A. bisporus*, cultivated button mushrooms (12), and inhibit the growth of *Pseudogymnoascus destructans*, the causative agent of white nose syndrome in bats (93).

For pest control, 1-octen-3-ol is used as a lure to attract certain species of mosquitoes and biting flies (e.g., no-see-ums, family: Ceratopogonidae) in or on electronic bug killer stations (30). 1-Octen-3-ol found in human sweat attracts insect species such as *Anopheles gambiae*, thus functioning as a host cue (61).

Laboratory Studies of VOC Toxicity

In nature, volatiles do not occur alone, but in the laboratory, we have the opportunity to study them one by one, or in small combinations, in systems that can elucidate their possible toxicities and other physiological effects. Several groups have used controlled in vitro assays to assess the toxicological potential of selected biogenic VOCs.

An in vitro cytotoxicity assay using a human lung carcinoma epithelial cell line tested 13 VOCs, of which the 3 most toxic volatiles were 1-decanol, 1-octen-3-ol, and 3-octenal (68). The same VOCs were further tested for their ability to damage DNA and cause mutagenic effects in cognate in vitro systems. DNA damage was observed at concentrations in which cytotoxic effects were found, but no mutagenic effects were detected (67). In contrast, when common VOCs were tested for SOS-inducing activity, 1-octen-3-ol, 3-octanol, and 3-octanone showed positive or pseudo-positive effects; and 3-methyl-2-butanone and 3-methyl-2-butanol were mutagenic in the Ames test assay (85). Our laboratory has utilized human embryonic cells as a humanized model and found that vapors of 1-octen-3-ol were 80 times more toxic than toluene in this system (48). Similarly, n-octanal, nonanal, and 2-ethyl-1-hexanol showed higher toxicities than that of toluene in human neuroblastoma SK-N-SH cells and primary cultured rat neurons (125).

In vivo animal studies to test the toxicity of fungal VOC are limited. In early exposures studies with rats, gas phase 3-methylfuran caused damage to airway epithelium with pneumonitis and necrotizing suppurative rhinitis (35). Using a murine model, it was determined that exposure to vapors of both 1-octen-3-ol and 3-octanol decreased respiratory rate (64).

To understand the acute effects of fungal VOCs possibly associated with sick building syndrome (38), a Swedish group used human volunteers to test some of the VOCs predominantly present in water-damaged indoor environments. Inhalation of 10 mg/m^3 of 1-octen-3-ol caused nose, throat, and eye irritation and headaches in these volunteers; the nasal lavage showed an increase in inflammatory biomarkers such as eosinophil cationic protein, myeloperoxidase, and lysozyme (121). Similarly, exposure to 1 mg/m^3 of 3-methylfuran in human volunteers led to a significant increase in blinking frequency and decreases in the forced vital capacity of lung, along with increases in the inflammatory markers myeloperoxidase and lysozyme (120).

In our laboratory, we have used a *Drosophila melanogaster* model to demonstrate that 1-octen-3-ol, 2-octanone, 2-octanol and *trans*-2-octanol caused toxicity, locomotory defects, and changes in green fluorescent protein–labeled dopaminergic neurons (47). Exposure of *Drosophila* to 1-octen-3-ol vapors resulted in loss of dopamine neurons and inhibition of the uptake of dopamine via vesicular monoamine transporter (VMAT) (46). This study may provide insight into a Parkinson disease–like condition reported in human populations after exposure to water-damaged moldy buildings (29). Furthermore, low concentrations of 1-octen-3-ol induced a nitric oxide (NO)-mediated inflammatory response in hemocytes (45). Finally, the *Drosophila* test also has provided a bioassay for assessing the toxicological effects of VOCs emitted by a variety of common molds, including those isolated after hurricanes (48, 126, 129), and for studying the virulent effects of VOCs synthesized by the medically important species *A. fumigatus* (4).

PERSPECTIVES AND PREDICTIONS

Fungal VOCs present many challenges. Their enormous heterogeneity—chemically, spatially, and temporally—combined with their low concentrations and innate evaporative properties makes them difficult to study in the field or laboratory. Each species of fungus emits a unique profile of different VOCs that varies qualitatively and quantitatively with the producing species, the age of the fungal colony, water availability, type of substrate, temperature, presence of interacting species, and other environmental parameters. Scientists in different disciplines, most of whom do not publish in the same journals nor attend the same meetings, study disparate aspects of their detection, olfactory impact, and physiological effects. One cannot help but be reminded of the parable of the blind men and the elephant: Depending on the subdiscipline, scientists focus on different parts of the VOC elephant, making it difficult to see the whole. We need more interdisciplinary work in order to investigate the complexities of the biological role of VOCs, and we need scientists to recognize that their experimental focus on liquid-phase biochemistry overlooks important aspects of cellular communication conducted through the air (**Figure 1**).

While hundreds of VOCs associated with molds and mushrooms have been chemically identified, we are only now beginning to understand their functionality. The study of biogenic VOCs and

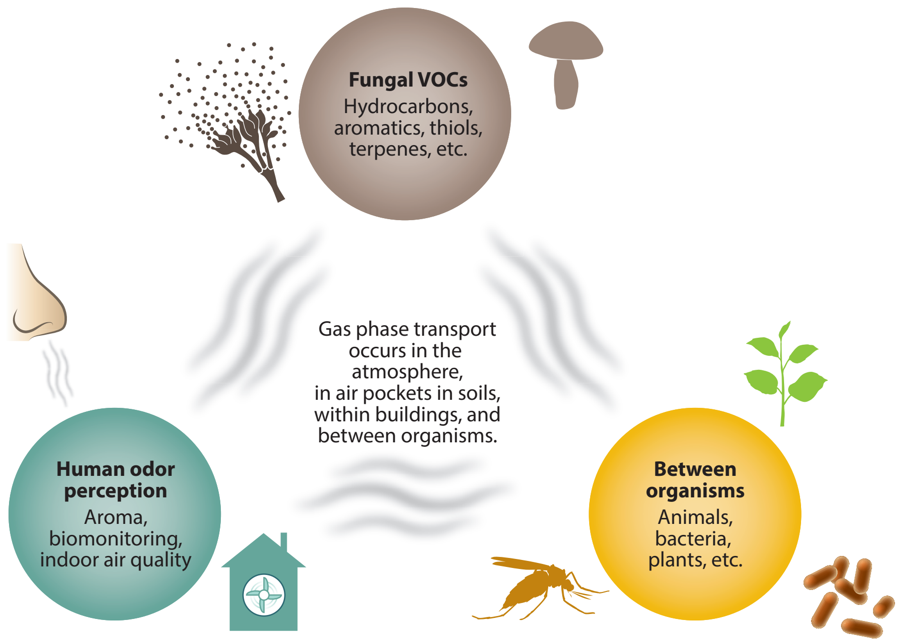

Figure 1

Fungal volatile organic compounds (VOCs) are important as aroma compounds and signaling agents that are easily transmitted through the atmosphere.

their roles in interkingdom communication, cellular signaling, and human health represent a new biological frontier. Intra- and interorganism volatile-mediated signaling is more common, more important, and more complicated than most biologists recognize. Perhaps this review will encourage scientists to pay more attention to the odor compounds emitted by the microbes they study.

SUMMARY POINTS

1. As analytical techniques have improved, several hundred different compounds have been identified as fungal VOCs.
2. Fungi are highly polymorphic in their ability to produce VOCs. In addition to genotypic variability between strains and species, VOC profiles are influenced by the physical environment and many biotic factors. For any given fungus, the profiles change with developmental stage of the fungus and with the associated microbiota.
3. Much of the research on volatiles has focused on their sensory properties in food and flavor or their identification as indirect assays for fungal growth.
4. Several oxylipins associated with mold metabolism, especially 1-octen-3-ol, function as intra- and interspecific signaling agents. Biological activity is sensitive to the concentration of the VOC; high concentrations, such as those associated with confined spaces, can be toxic.
5. The functionality of fungal and other microbial volatiles is an understudied aspect of cellular communication and constitutes an important frontier in microbiology.

DISCLOSURE STATEMENT

The authors are not aware of any affiliations, memberships, funding, or financial holdings that might be perceived as affecting the objectivity of this review.

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