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Volatile sesquiterpenes from fungi: what are they good for?

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Abstract Fungi can be found in almost all sorts of habitats competing with an even higher number of other organisms. As a consequence fungi developed a number of strategies for protection and communication with other organisms. This review focuses on the increasing number of volatile sesquiterpenes found to be produced by fungal species. The remarkable diversity of this type of volatile organic compound (VOC) within the kingdom fungi is presented and their benefits for the fungi are discussed. The majority of these compounds are hydrocarbons comprising several dozens of carbon skeletons. Together with oxygenated sesquiterpenes they include compounds unique to fungi. Only in recent years the interest shifted from a mere detection and characterization of compounds to their biological function. This review reveals highly diverse ecological functions including interactions with bacteria, other fungi, insects and plants. VOCs act as autoinducer, defend against competing species and play essential roles in attracting pollinators for spreading fungal spores. For many sesquiterpene VOCs sophisticated responses in other organisms have been identified. Some of these interactions are complex involving several partners or transformation of the emitted sesquiterpene. A detailed description of ecological functions of selected sesquiterpenes is given as well as their potential application as marker molecules for detection of mould species. Structures of all described sesquiterpenes are given in the review and the biosynthetic routes of the most common skeletons are presented. Summarizing, this article provides a detailed overview over the current knowledge on fungal sesquiterpene VOCs and gives an outlook on the future developments.

Keywords Chemical ecology · Chemodiversity · Fungi · Sesquiterpenes · Volatile organic compounds

Introduction

Fungi and bacteria are known to produce a wealth of secondary metabolites (e. g. Brakhage and Schroeckh 2011). Higher fungi are characterised by the production of macroscopic fruiting bodies to generate and to distribute their spores. These fruiting bodies are under constant threat of other organisms feeding on them. As a consequence these organisms developed a number of strategies for protection and communication with other organisms (Rohlfs and Churchill 2011). The fungal phylum Basidiomycota produces many sesquiterpenes via humulane which is then transformed and rearranged to a multitude of compounds (Abraham 2001). There appears to be

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continuing interest in the overall chemistry of fungi because this group of eucarya is arguably still among the world's greatest unexplored resources for chemodiversity (Smedsgaard and Nielsen 2005). A still increasing number of fungal metabolites have been described and hundreds of terpenes have been isolated from the kingdom fungi, most of them are sesquiterpenes. Sesquiterpenes are not very volatile compared to other organic compounds but modern analytics can detect and monitor many of them in the environment (Duhl et al. 2007). However, not only our analytical equipment allows the detection of many sesquiterpenes in air samples but also highly sophisticated receptor proteins, found in a multitude of highly diverse organisms, can do the same and lead to ecological responses (Unsicker et al. 2009).

The review comprises fungal sesquiterpenes which have been extracted from the gas phase sufficient volatile to be recognized by other organisms. Conventional sample preparation techniques are mainly steam distillation and solvent extraction. The extracts are further chromatographically fractionated and compounds are identified by MS or NMR techniques. Volatile terpenes from fungi were first described in 1963 (Sprecher 1963; Hanssen 2002). In a laboratory steam distillation setup, steam passes through the fungal material and takes volatile organic compounds with it. The mixture of steam and VOCs is then induced in a condenser and the resulting distillate contains the fungal volatiles. For lower yields or very delicate compounds in the fungi, solvent-based extraction methods are used. The fungal material is repeatedly washed with a solvent (e.g. hexane or pentane) and the resulting solution contains dissolved fungal volatile metabolites. Further filtration and distillation processes make up a concentrate from which the compounds can be extracted. The disadvantages of these conventional extraction methods are that they may destroy some delicate compounds and introduce artefacts through decomposition of the matrix or by the solvent itself. Additionally, these techniques are time-consuming and may need the use of highly toxic organic solvents (Risticevic et al. 2009). In our days the standard extraction methods are sorbent-based in which the volatiles are unspecifically collected on sorbent traps. Among these, solid-phase microextraction (SPME) is the favorite method today. Its relatively easy handling and short preparation times (preconcentration and sample introduction in one step) made it an attractive tool for sensorial and analytical chemistry. It can be used on-site and displays an absolutely non-invasive extraction method. An outlook on new developments in sorbent-based extractions is given in the end of this article.

This review focuses on sesquiterpenes which are volatile and remarkable concerning their chemotaxonomical, ecological and pharmaceutical implications. These are mainly sesquiterpene-hydrocarbons, monooxygenated sesquiterpenes and sesquiterpene-ketols. The diversity of volatile sesquiterpenes reported from fungi and their application for monitoring of moulds will be presented. Finally, the ecological function of several of these sesquiterpenes will be discussed revealing an incredible wealth of species-species interactions many of them being highly specific and relying on well defined mixtures of volatiles.

Volatile sesquiterpenes from fungi

Fungi produce a number of volatile organic compounds (VOCs) comprising aliphatic and aromatic hydrocarbons, esters, ketones, aldehydes, alcohols and mono-, sesqui- and diterpenes. Volatile sesquiterpenes have almost exclusively been reported from the subkingdom Dicarya, also called higher fungi (Hibbett et al. 2007), i. e. Ascomycota and Basidiomycota. Ascomycota are characterized by the ascus (sac) a microscopic sexual structure in which the ascospores are formed. Basidiomycota reproduce sexually by forming specialized cells, known as basidia. The basidia bear the basidiospores. Some Ascomycota and to a lesser extent Basidiomycota do not form spores and are asexual. They have formerly been placed into the Deuteromycota but are now identified by phylogenetic analyses of their DNA (James et al. 2006).

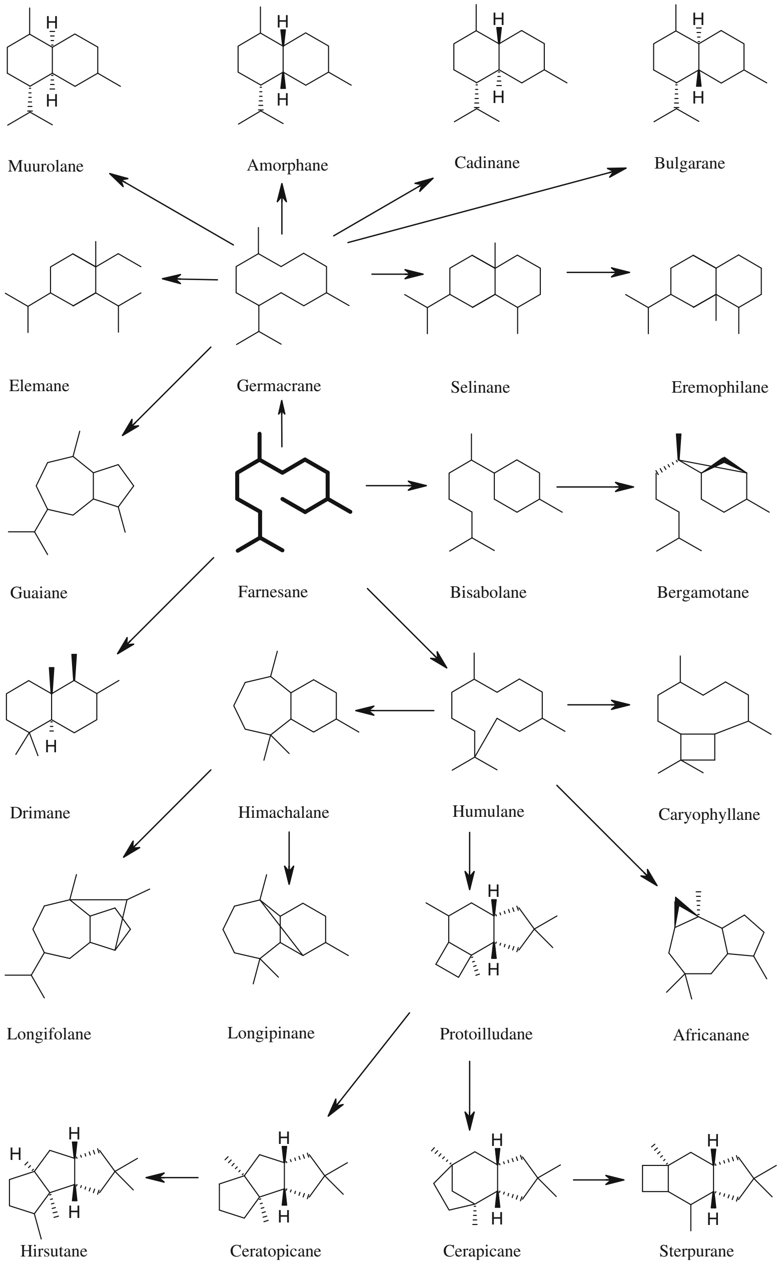
The volatile fraction of sesquiterpenes produced by fungi consists mostly of hydrocarbons possessing a multitude of different carbons skeletons. Starting from farnesol-pyrophosphate the sesquiterpene skeleton is cyclised by different sesquiterpene cyclases (Cane 1990; Benedict et al. 2001). The first step is the removal of the pyrophosphate. The resulting highly reactive carbocation is stabilized by the enzyme and channelled to intermediates often leading to several products (Steele et al. 1998; Pichersky et al. 2006). Important intermediate sesquiterpene skeletons are humulane and germacrane which are the branching points for several other sesquiterpene types (Fig. 1) as has been shown for *Penicillium roqueforti* (Calvert et al. 2002). Sesquiterpenes are usually formed by fungi in the late growth phase. The formation of volatile sesquiterpenes is often based on enzymes expressed in differentiated cells. The resulting metabolites are modulated by other enzymes which are induced by environmental stress factors. Little is known about the specific mechanisms in fungi but from plants several environmental factors, including UV-radiation (Back et al. 1998), infection (Townsend et al. 2005) and herbivore attack (Yuan et al. 2008), have been identified which lead to the enhanced production of volatile sesquiterpenes.

Many species of the phylum Ascomycota have been reported to produce volatile sesquiterpenes (Table 1). Caryophyllene (**61**) was detected from *Phialophora fastigata* and α-curcumene (**15**) (Fig. 2) from *Penicillium commune* and *Paecilomyces variotii* (Sunesson et al. 1995). The acyclic sesquiterpenes α-farnesene (**1**) and trans-β-farnesene (**2**) have been found in *Aspergillus fumigatus* and the cyclic sesquiterpene γ-curcumene (**16**) was obtained from *Aspergillus versicolor*. Germacrene B (**11**) and α-longipinene (**88**) were produced by *Paecilomyces variotii* (Sunesson et al. 1995). Trans-β-bergamotene (**67**) has been detected in *Aspergillus fumigatus* (Nozoe et al. 1976a) and *Pseudeurotium ovale* (Cane and King 1976), both producers of bisabolane-antibiotics. From *Aspergillus terreus* the sesquiterpene hydrocarbons γ-cadinene (**29**) and aristolochene (**58**) has been reported (Cane et al. 1987). Two unidentified sesquiterpene hydrocarbons have been detected in the ascomycete *Beauveria bassiana* (Crespo et al. 2008) and unidentified sesquiterpenes have been found in *Aspergillus versicolor*, *Penicillium commune*, *Cladosporium cladosporioides*, *Paecilomyces variotii*, and *Phialophora fastigata* (Sunesson et al. 1995).

The genus *Penicillium* belongs to the phylum Ascomycota and is known for the production of many secondary metabolites. Since many strains have distinct smells it is not surprising that volatile sesquiterpenes have been detected as well. Germacrene A (**10**) is produced by *Penicillium cyclopium,* germacrene B (**11**) by *Penicillium expansum,* β-elemene (**14**) and a δ-guaiene-like sesquiterpene hydrocarbon by *Penicillium clavigerum* (Fischer et al. 1999) and β-caryophyllene (**61**) and an unidentified sesquiterpene came from *Penicillium caseifulvum* (Larsen, 1998). Not sufficient strains have been analyzed to decide whether some of these compounds are discriminative for these *Penicillium* species. *Penicillium roqueforti* used to produce the famous Roquefort cheese, synthesizes a large number of volatile compounds and sesquiterpenes with a rich diversity of carbon skeletons. Among the identified volatiles from *Penicillium roqueforti* were the sesquiterpenes β-patchoulene (**95**), a β-elemene-isomer, β-elemene (**14**), diepi-α-cedrene (**97**), β-gurjunene (**103**), a β-patchoulene-isomer, aristolochene (**58**), valencene (**59**), α-selinene (**48**), β-himachalene (**64**), α-chamigrene (**77**), β-bisabolene (**18**) and α-panasinsene (**98**) (Jelen 2002). In another study these sesquiterpene hydrocarbons were confirmed and in addition caryophyllene (**61**), β-chamigrene (**78**) and germacrene A (**10**) were reported (Demyttenaere et al. 2003). The authors could also show that *P. roquefortii* strains producing PR toxin and sporogen AO-1 produced also high amounts of aristolochene while toxin-free strains are characterized by high amounts of two unidentified sesquiterpene hydrocarbons. *Penicillium aurantiogriseum* produced a number of volatile sesquiterpenes when grown on different substrates but none of the terpenes have been identified (Börjesson et al. 1990).

The hydrocarbon α-gurjunene (**102**) has been identified in an ascomycetous *Gliocladium* sp. (Stinson et al. 2003) and an unusual rearranged sesquiterpene hydrocarbon 2,7-dimethyl-1-isopropylnaphthalene (**55**), probably derived via Wagner-Meerwein rearrangement from a cadinane-like precursor, has been isolated from *Daldinia concentrica* (Qina et al. 2006). A number of volatile sesquiterpenes from the ascomycete *Trichoderma atroviride* have been detected among them α-farnesene (**1**), β-farnesene (**2**), nerolidol (**5**), γ-curcumene (**16**), α-zingiberene (**19**), β-bisabolene (**18**) and α-bergamotene (**65/66**) (Stoppacher et al. 2010). The ascomycete *Ascocoryne sarcoides* is an endophyte from Patagonia and produces a variety of volatile organic compounds that have been suggested as fuel alternatives, termed myco-diesel. Several of these strains produced considerable amounts of sesquiterpenes as well and one strain produced no less than 49 different sesquiterpenes, however, none of them has been identified (Griffin et al. 2010).

Fig. 1 Biosynthetic routes of the most common skeletons of volatile sesquiterpenes from fungi starting from the farnesane skeleton (in bold)



Trichodiene (**71**) was first isolated from the toxin producing ascomycete *Trichothecium roseum* (Nozoe and Machida 1972). It was later also found in *Stachybotrys chartarum* (Wilkins 2000). *Stachybotrys* species also produce *β*-farnesene (**2**), α-curcumene (**15**), *β*-bisabolene (**18**) and cuparene (**75**). From *Trichothecium roseum* *β*-acoradiene (**83**), *β*-santalene (**68**), α-(**77**) and *β*-chamigrene (**78**), α-curcumene (**15**), *β*-bisabolene (**18**), and trichodiene (**71**) were detected while *Fusarium sporotrichioides* produced *β*-chamigrene (**78**) and trichodiene and *Fusarium culmorum* only trichodiene (Wilkins et al. 2003). A complex mixture of sesquiterpenes have been found in *Fusarium sambucinum* and α-farnesene (**1**), *β*-farnesene (**2**), ar-cucumene (**15**), *β*-bisabolene (**18**), *β*-selinene (**49**), *β*-himachalene (**64**), α-bergamotene (**65/66**), *β*-santalene (**68**), trichodiene (**71**), *β*-chamigeren (**78**), acoradiene (**83**) and diepi-α-

Table 1 Volatile sesquiterpenes from Ascomycota

Organism	Subphylum, class	Volatile sesquiterpenes	References
Ascocoryne comprises saprobic fungi growing on dead wood			
Ascocoryne sarcoides	Pezizomycotina, Leotiomycetes	X	Griffin et al. (2010)
Aspergillus grows saprotrophic in soil and on decaying organic matter; comprises also human pathogens			
*Aspergillus fumigatus**	Pezizomycotina, Eurotiomycetes	**1, 2, 3, 67**	Sunesson et al. (1995) Nozoe et al. (1976a) Dichtl et al. (2010)
*Aspergillus versicolor**	Pezizomycotina, Eurotiomycetes	**16**, X	Sunesson et al. (1995)
*Aspergillus terreus**	Pezizomycotina, Eurotiomycetes	**29, 58**	Cane et al. (1987)
Beauveria grows in soil and is pathogenic for many arthropods			
Beauveria bassiana	Pezizomycotina, Sordariomycetes	X	Crespo et al. (2008)
Candida species are commensals or endosymbionts of animals and humans, some are pathogens			
Candida albicans	Saccharomycotina, Saccharomycetes	**3**	Langford et al. (2009)
Candida dubliniensis	Saccharomycotina, Saccharomycetes	**3**	Hornby et al. (2001)
Ceratocystis species are plant pathogens mainly infecting trees			
Ceratocystis coerulescens	Pezizomycotina, Sordariomycetes	**3**, **5**, **6**, **7**	Sprecher et al. (1975)
Ceratocystis piceae	Pezizomycotina, Sordariomycetes	**105**, **108**, **109**	Hanssen et al. (1986a, b, c) Hanssen and Abraham (1988)
Ceratocystis populina	Pezizomycotina, Sordariomycetes	**26**, **27**, **30**, **39**, **40**	Hanssen (1985a)
Cladosporium are indoor and outdoor molds forming dark colonies, some are plant pathogens			
*Cladosporium cladosporioides**	Pezizomycotina, Dothideomycetes	X	Sunesson et al. (1995)
Daldinia (coal fungus) grows saprotroph on decaying wood			
Daldinia concentrica	Pezizomycotina, Sordariomycetes	**55**	Qina et al. (2006)
Fusarium species are widespread in soil and plants, some species are plant and human pathogens			
*Fusarium culmorum**	Pezizomycotina, Sordariomycetes	**71**	Wilkins et al. (2003)
*Fusarium oxysporum** (in bacterial association)	Pezizomycotina, Sordariomycetes	**9**, **61**	Minerdi et al. (2009)
*Fusarium sporotrichioides**	Pezizomycotina, Sordariomycetes	**71**, **78**	Wilkins et al. (2003)
Fusarium sambucinum	Pezizomycotina, Sordariomycetes	**1**, **2**, **15**, **18**, **49**, **64**, **65/66**, **68**, **71**, **78**, **83**, **97**, X	Jelén et al. (1995)
Gliocladium is a plant endophyte, some species are pathogens for other fungi and nematodes			
Gliocladium sp.	Pezizomycotina, Sordariomycetes	**102**	Stinson et al. (2003)

Table 1 continued

Organism	Subphylum, class	Volatile sesquiterpenes	References
Helminthosporium comprises several plant pathogens and toxin producing species			
Helminthosporium sp.	Pezizomycotina, Dothideomycetes	**12**, **100**, **113**	Dorn and Arigoni (1974) Winter et al. (1990)
Hypomyces is a genus living parasitic on other fungi			
Hypomyces odoratus	Pezizomycotina, Sordariomycetes	**60**	Kühne et al. (1991)
Leptographium lives on decaying wood and comprises several plant pathogens			
Leptographium lundbergii	Pezizomycotina, Sordariomycetes	**89**, **90**, **91**	Abraham et al. (1986)
Muscodor is a tropical genus producing many volatile organic compounds inhibiting other fungi			
Muscodor albus	Pezizomycotina, Sordariomycetes	**17**, **26**, **49**, **59**, **61**, **78**, **79**, **80**, **96**	Strobel et al. (2001)
Paecilomyces is a genus of nematode infecting and killing fungi			
*Paecilomyces variotii**	Pezizomycotina, Eurotiomycetes	**11**, **15**, **88**, X	Sunesson et al. (1995)
Penicillium lives in soil, many species are used for food or antibiotics production			
Penicillium caseifulvum	Pezizomycotina, Eurotiomycetes	**61**, X	Larsen (1998)
Penicillium clavigerum	Pezizomycotina, Eurotiomycetes	**14**, δ-guaiene-like hydrocarbon	Fischer et al. (1999)
*Penicillium commune**	Pezizomycotina, Eurotiomycetes	**15**, X	Sunesson et al. (1995)
Penicillium cyclopium	Pezizomycotina, Eurotiomycetes	**10**	Fischer et al. (1999)
*Penicillium decumbens**	Pezizomycotina, Eurotiomycetes	**2**, **64**, **74**, **75**, **77**, **78**, **83**, **86** and others	Polizzi et al. (2011)
*Penicillium expansum**	Pezizomycotina, Eurotiomycetes	**11**	Fischer et al. (1999)
*Penicillium roquefortii**	Pezizomycotina, Eurotiomycetes	**10**, **14**, **18**, **48**, **58**, **59**, **61**, **64**, **77**, **78**, **95**, **97**, **98**, **103**	Jelen (2002) Demyttenaere et al. (2003)
Phialophora comprises parasitic and saprophitic species			
*Phialophora fastigata**	Pezizomycotina, Dothideomycetes	**61**, X	Sunesson et al. (1995)
Pseudeurotium lives in soil and produces several bioactive compounds			
Pseudeurotium ovale	Pezizomycotina, Leotiomycetes	**67**	Cane and King (1976)
Sclerotinia comprises several plant pathogens and parasites			
Sclerotinia minor	Pezizomycotina, Leotiomycetes	**5**	Fravel et al. (2002)
Stachybotrys grows on cellulose-rich materials and is an indoor pollutant			
*Stachybotrys chartarum**	Pezizomycotina, Sordariomycetes	**71**	Wilkins (2000)
Stachybotrys sp.	Pezizomycotina, Sordariomycetes	**2**, **15**, **18**, **75**	Wilkins et al. (2003)
Trichoderma can be found in all soils and comprises many avirulent plant symbionts			
*Trichoderma atroviride**	Pezizomycotina, Sordariomycetes	**1**, **2**, **5**, **16**, **19**, **18**, **65/66**	Stoppacher et al. (2010)

Table 1 continued

Organism	Subphylum, class	Volatile sesquiterpenes	References
Trichothecium grows on decaying plant material but is also a pathogen for many plants			
Trichothecium roseum	Pezizomycotina, Sordariomycetes	**15**, **18**, **68**, **71**, **77**, **78**, **83**	Nozoe and Machida (1972) Wilkins et al. (2003)

Sesquiterpene numbers (in bold) correspond to compounds in Figs. 2, 3, 4, 5, 6 (X = unidentified volatile sesquiterpene)

The additional mark * indicates important indoor mould species related to building dampness

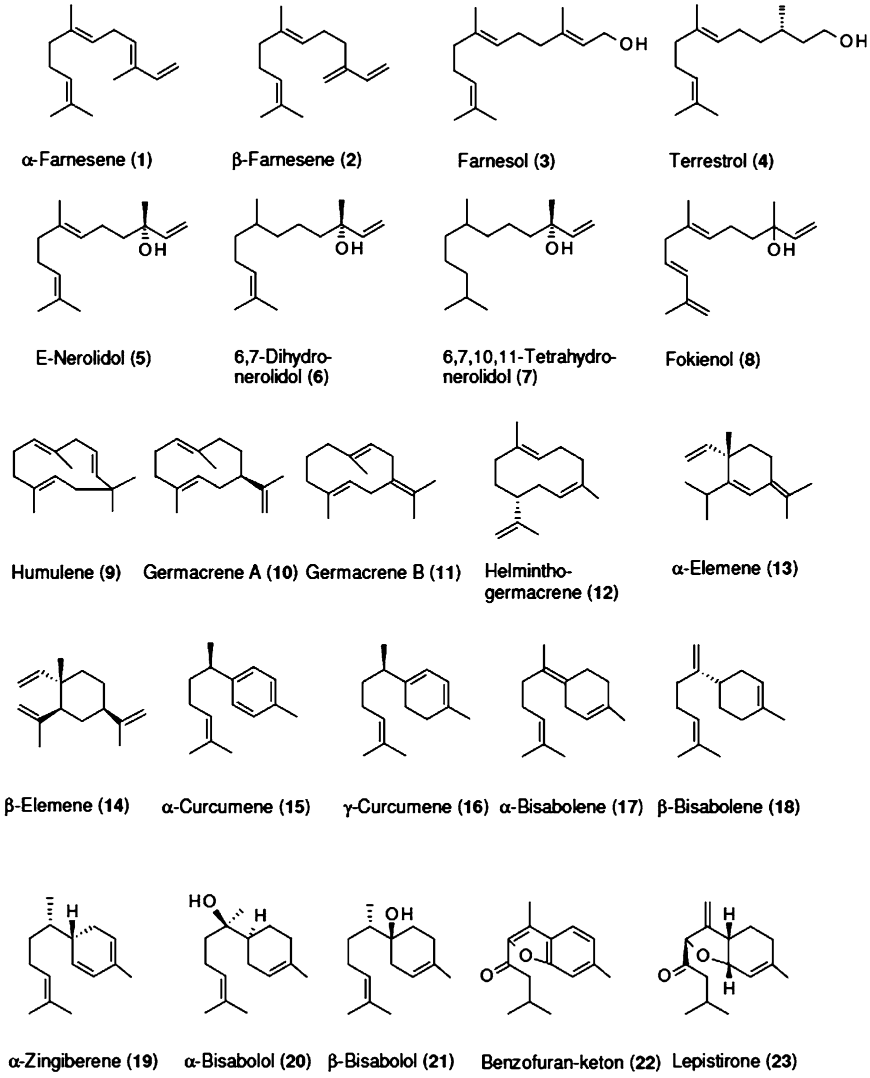


Fig. 2 Acyclic and monocyclic volatile sesquiterpenes detected in fungi

cedrene (**97**) have been reported besides some unidentified sesquiterpene hydrocarbons (Jelén et al. 1995). In a number of *Fusarium* species it has been shown that the formation of trichodiene is correlated with the production of trichothecin toxins (Jelen et al. 1997). Interesting is the report on the screening of several fungi for the presence of trichodiene synthases. Although trichothecenes production has been reported for species of the genera *Myrothecium, Stachybotrys, Trichoderma* and *Trichothecium* only strains of *Myrothecium* and *Stachybotrys* gave strong positive reactions (Fekete et al. 1997). Possible reasons may be misidentifications of the metabolites or larger differences in the synthase genes leading to the failure of the PCR reaction. However, a recent report pointed more to a tighter clustering of trichothecin producers within a given genus which would require more species to be tested from these five genera in order to get a better resolution before a final conclusion can be drawn (Koster et al. 2009). From another toxin producing ascomycetous genus, *Helminthosporium*, sativene (**100**), longifolene (**113**) (Dorn and Arigoni 1974) and helminthogermacrene (**12**) (Winter et al. 1990) has been isolated. The very rare helminthogermacrene has later also been detected in the liverwort plant *Scapania undulata* and in *Santalum album*.

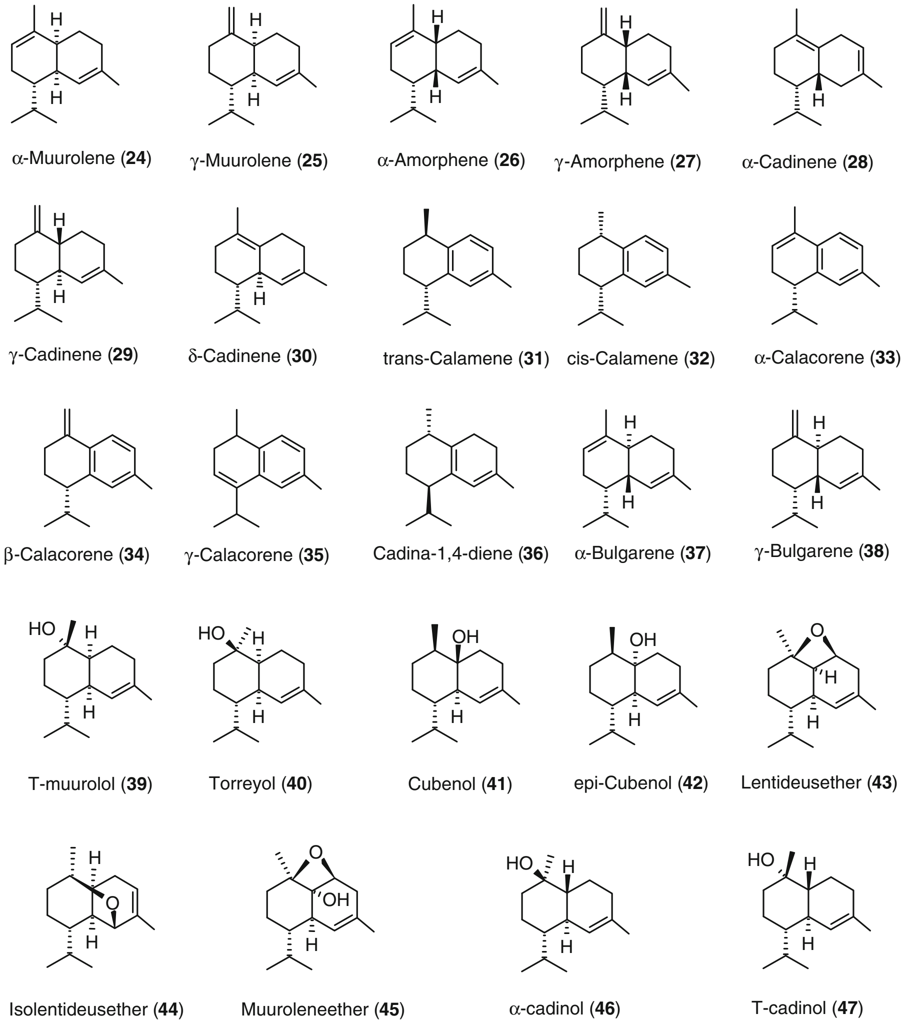
The sesquiterpene africanol with the novel africanane skeleton has been characterized from the soft coral *Lemnalia africana* (Tursch et al. 1974) but was later also reported from a few plants. Finally, alcohols with this very unusual skeleton have been isolated and characterized from the ascomycete *Leptographium lundbergii* isolated from decaying wood. Intensive NMR analyses led to the structures of leptographiol (**89**), isoleptographiol (**90**) and isoafricanol (**91**) (Abraham et al. 1986). They are still the only africananes known from fungi and as has been shown for many other fungal metabolites their formation and ratios depend on the culture conditions (Abraham et al. 1987). The acyclic sesquiterpene alcohol E-nerolidol (**5**) is produced by *Sclerotinia minor* (Fravel et al. 2002).

A triquinane intermediate has been postulated for a long time as an intermediate in the biosynthesis from the protoilludane skeleton to hirsutane sesquiterpenes but it has long not been detected. Finally, it was found in *Ceratocystis piceae*, a species which does not belong to the Basidiomycotina but to the Ascomycotina. *Ceratocystis piceae* is still the only fungus outside the Basidiomycotina possessing protoilludane derived sesquiterpenes, long seen as a biomarker for Basidiomycotina. The novel sesquiterpene alcohol from *Ceratocystis piceae* was named ceratopicanol (**105**) and the parent hydrocarbon ceratopicane (Hanssen and Abraham 1988). The structure and the absolute configuration of ceratopicanol were confirmed by total synthesis starting from (R)-(+)-limonene (Mehta and Karra 1991). No biological activity could yet be found for ceratopicanol. A second metabolite of the ceratopicane series was identified in *Macrocystidia cucumis*, a basidiomycete (Hellwig et al. 1998). It is the α,β-unsaturated ketone cucumin H (**106**) which did not display antimicrobial or cytotoxic activities. Interestingly, the carbon skeleton of cucumin H is enantiomeric to that of ceratopicanol.

As the biosynthesis of hirsutanes the biosynthesis of sterpuranes and bulleranes requires a tricyclic intermediate between protoilludane and those sesquiterpenes and again this intermediate carbon skeleton has not been found for a long time. Up to now still no metabolite possessing this postulated carbon skeleton was detected in Basidiomycota. The ascomycete *Ceratocystis piceae* which already provided the other long sought skeleton ceratopicanane also produced this carbon frame. It was isolated and characterized from this fungus together with Δ6-protoilludene (**109**) (Hanssen et al. 1986b). The alcohol was named cerapicol (**108**) and the hydrocarbon cerapicane (Hanssen and Abraham 1988). It came as a complete surprise to isolate two long postulated carbon skeletons, cerapicane and ceratopicane, from one ascomycete which, furthermore, was the first species of the Ascomycota producing sesquiterpenes derived from protoilludane. No antibiotic, phytotoxic or other biological activities were found for cerapicol. Another species of this genus, *Ceratocystis coerulescens*, did not give any of these compounds but the acyclic sesquiterpenes farnesol (**3**), trans-nerolidol (**5**), dihydro-nerolidol (**6**), tetrahydro-nerolidol (**7**) and dihydrofarnesyl acetate (Sprecher et al. 1975). From *Ceratocystis populina* came T-muurolol (**39**), α-(**26**) and γ-amorphene (**27**), δ-cadinene (**30**) and δ-cadinol (= torreyol) (**40**) (Hanssen 1985a) (Fig. 3).

Many of us use to enjoy fruiting bodies of Basidiomycota in our food and have noticed the distinct smells of individual species. Volatile sesquiterpenes often contribute to the characteristic smell of species and several sesquiterpenes have been identified in the phylum Basidiomycota (Table 2). The genus *Lactarius* harbours a number of edible mushrooms and is rich in secondary metabolites many belonging to the class of sesquiterpenes. Among the volatile sesquiterpenes identified from this genus is humulene (**9**) found in *Lactarius mitissimus* (Lin and Ji-Kai 2002; Liu 2007). *Lactarius camphoratus*

Fig. 3 Volatile sesquiterpenes of the muurolane and cadinane group from fungi



produces a sesquiterpenepoxide which has been identified as 12-hydroxycaryophyllene-4,5-epoxide (**62**) (Daniewski et al. 1981). No biological activities were reported for this metabolite.

The sesquiterpene hydrocarbons δ-cadinene (**30**) and cis-calamene (**32**) are formed by *Sclerotium rolfsii* (Fravel et al. 2002). The related species, *Coprinopsis cinerea* (formerly *Coprinus cinereus*), produces the hydrocarbons pentalenene (**107**), α-muurolene (**24**), α-cuprenene (**74**) and δ-cadinene (**30**) (Agger et al. 2009). The rare sesquiterpene hydrocarbon hirsutene (**104**) has been reported from *Stereum consors* (Nozoe et al. 1976b) and *Lentinus crinitus* (Abate and Abraham 1994).

Sesquiterpenes with the bisabolane skeleton are mainly known from plants but rare in fungi. Lepistirone (**23**) is one of these bisabolane sesquiterpenes formed by *Lepista irina* (Abraham et al. 1991). From another *Lepista* species, *Lepista nuda,* the hydrocarbons α-(**17**) and β-bisabolene (**18**) have been identified (Audouin et al. 1989). *Cystostereum murraii* forms the unusual benzofuran-keton (**22**) with the bisabolane skeleton (Abraham and Hanssen 1987) and *Phlebia radiata* α-bisabolol (**20**) (Gross et al. 1989).

Fruiting bodies of the basidiomycete *Lentinus lepideus* possess a characteristic anise-like odour. From the fungus α-copaene (**92**), α-elemene (**13**), β-farnesene (**2**), α-(**24**) and γ-muurolene (**25**), δ-cadinene (**30**), cadina-1,4-diene (**36**), α-calacorene (**33**) and two unidentified sesquiterpene hydrocarbons have been isolated (Hanssen 1982). This fungus also

Table 2 Volatile sesquiterpenes from Basidiomycota, subphylum Agaricomycotina, class Agaricomycetes

Organism	Volatile sesquiterpenes	References
Chondrostereum pupureum infects Rosaceae, esp. *Prunus*, (silver leaf infection)		
Chondrostereum purpureum	**111**	Ayer and Saeedi-Ghomi (1981)
Clitocybe decomposes ground litter in forests, some species are edible		
Clitocybe conglobata	**57**	Xu et al. (2009)
Clitocybe illudens	**40**	Nair and Anchel (1973)
Coprinopsis autodigests the lamellae to release the spores (inky cap)		
Coprinopsis cinerea	**24**, **30**, **74**, **107**	Rasser et al. (2000)
Cortinarius is a huge genus showing a veil between the stem and the cap when young		
Cortinarius odorifer	**40**	Egli et al. (1988)
Cystoderma carcharias grows on soils of coniferous forests		
Cystoderma carcharias	**5**	Wu et al. (2005)
Cystostereum murraii grows on dead wood and fallen trunks		
Cystostereum murraii	**22**	Abraham and Hanssen (1987)
Fistulina hepatica grows on living or dead wood, preferably oaks		
Fistulina hepatica	**5**	Wu et al. (2007)
Fomitopsis grows on living or dead wood		
Fomitopsis insularis	**109**, **110**	Nozoe et al. (1977)
Fomitopsis pinicola syn. *Polyporus pinicola*	**2**, **5**, **24**, **25**, **26**, **27**, **29**, **30**, **31**, **34**, **42**, **46**, **61**, **84**, **86**, **87**, **88**, **92**, **94**, **93**, **100**, **109**, **113**	Rösecke et al. (2000)
Gloeophyllum grows on dead wood causing brown rot		
Gloeophyllum odoratum	**5**, **35**, **56**, **82**	Hanssen et al. (1986a, b, c) Rösecke et al. (2000)
Gloeophyllum sp.	**112**	Rasser et al. (2000)
Hypholoma is a woodland fungus growing on rotting wood and *Resinicium bicolor* is a plant pathogen causing white rot		
Hypholoma fasciculare and *Resinicium bicolor*	**24**, **25**, **26**, **27**, **28**, **29**, **37**, **38**	Hynes et al. (2007)
Inonotus obliquus (Chaga) causes white heart rot on trees, medicinal fungus		
Inonotus obliquus	**14**, **20**, **21**, **53**, **34**, **49**, **50**, **51**, **52**, **54**, **65**, **66**, **69**, **70**, **76**, **81**, **87**, **99**	Ayoub et al. (2009)
Lactarius grows saprophytic on wood litter and exudes a milky fluid when damaged		
Lactarius camphoratus	**62**	Daniewski et al. (1981)
Lactarius mitissimus	**9**	Lin and Ji-Kai (2002) Liu (2007)
Lactarius subumbonatus	**63**-6-hydroxystearate	Clericuzio et al. (1999)
Lentinellus grows on wood of hardwoods causing white rot		
Lentinellus cochleatus	**3**, **5**, **8**, **30**, **33**, **41**, **42**, **92**	Hanssen and Abraham (1986)
Lentinus grows on dead wood causing brown rot, also found indoors		
Lentinus crinitus	**104**	Abate and Abraham (1994)
Lentinus lepideus syn. *Neolentinus lepideus*	**2**, **3**, **4**, **13**, **24**, **25**, **30**, **33**, **36**, **39**, **40**, **41**, **42**, **43**, **44**, **45**, **46**, **47**, **56**, **92**	Hanssen (1985b) Abraham et al. (1988)
Lepista grows on organic litter on soil in woods		
Lepista irina	**23**	Abraham et al. (1991)

Table 2 continued

Organism	Volatile sesquiterpenes	References
Lepista nuda	**17**, **18**	Audouin et al. (1989)
Macrocystidia cucumis grows saprobic and terrestrial developing a strong odor		
Macrocystidia cucumis	**106**	Hellwig et al. (1998)
Phlebia radiata grows saprophytic on dead or weakened leaf trees		
Phlebia radiata	**20**	Gross et al. (1989)
Piptoporus betulinus grows as necrotrophic parasite on birch trees causing brown rot		
Piptoporus betulinus	**5**, **14**, **30**, **36**, **42**, **47**, **51**, **72**, **73**, **74**, **77**, **78**, **82**, **84**, **85**, **86**, **87**, **101**, **107**	Rösecke et al. (2000)
Sclerotium rolfsii is an omnivorous, soilborne pathogen, infecting many crops		
Sclerotium rolfsii	**30**, **32**	Fravel et al. (2002)
Stereum grows saprobic on leaves and all kinds of deadwood		
Stereum consors	**104**	Nozoe et al. (1976b)
Stereum sp.	**40**	Ainsworth et al. (1990)
Trametes grows saprobic on deadwood causing white rot and degrades lignin		
Trametes suaveolens	**5**, **87**	Rösecke et al. (2000)
Xylobolus grows saprobic on well decayed wood, mainly from oaks		
Xylobolus frustulatus	**40**	Van Eijk et al. (1984)

Sesquiterpene numbers (in bold) correspond to compounds in Figs. 2, 3, 4, 5, 6 (X = unidentified volatile sesquiterpene)

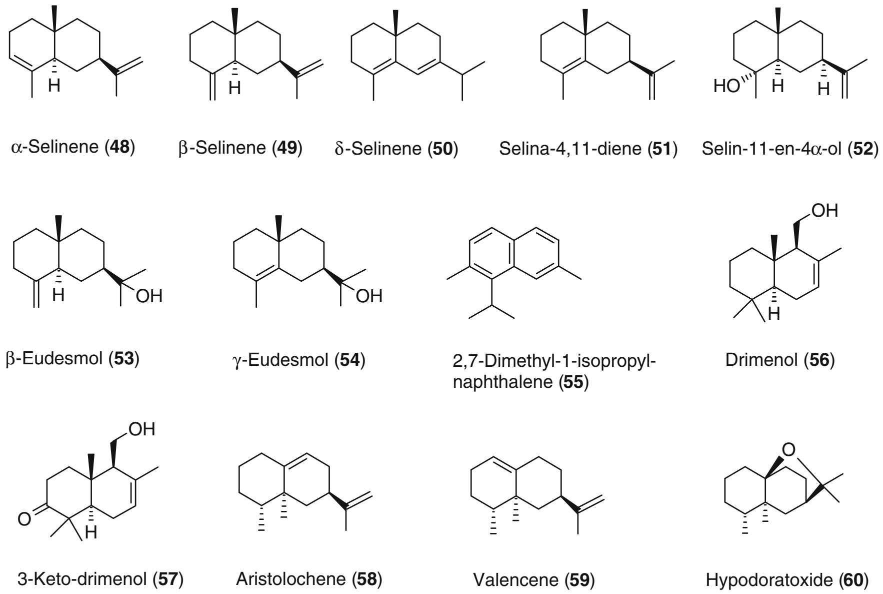
produces a number of volatile sesquiterpene alcohols and (−)-torreyol (**40**), (−)-T-muurolol (**39**), (+)-T-cadinol (**47**), α-cadinol (**46**), cubenol (**41**), epi-cubenol (**42**), farnesol (**3**) and drimenol (**56**) were identified (Hanssen 1985b). From the distillate the structures of four more oxygenated sesquiterpenes could be elucidated. Three of them possess the muurolane skeleton and are lentideusether (**43**), isolentideusether (**44**) and 10-hydroxy-lentideusether (**45**). The fourth oxygenated sesquiterpene detected in *Lentinus lepideus* is the acyclic terrestrol (**4**) (Abraham et al. 1988). Not many volatile sesquiterpene alcohols have been reported from fungi but the majority of them were detected in Basidiomycota. Drimenol (**56**) and trans-nerolidol (**5**) together with the hydrocarbons daucene (**82**) and γ-calacorene (**35**) are known from *Gloeophyllum odoratum* (Hanssen 1985a; Rösecke et al. 2000), torreyol (**40**) from *Clitocybe illudens* (Nair and Anchel 1973), β-barbatene (**87**) and trans-nerolidol (**5**) from *Trametes suaveolens* and pentalenene (**107**), α- (**84**) and β-cubebene (**85**), (S)-(−)-daucene (**82**), β-elemene (**14**), (+)-α-(**86**) and (−)-β-barbatene (**87**), β-bazzanene (**72**), isobazzanene (**73**), cyclobazzanene (**101**), cadina-1(6),4-diene (**36**), β-chamigrene (**78**), selina-4,11-diene (**51**), α-cuprenene (**74**), α-chamigrene (**77**), δ-cadinene (**30**), trans-nerolidol (**5**), T-cadinol (**47**) and 1-epi-cubenol (**42**) from *Piptoporus betulinus* (Rösecke et al. 2000). From *Lentinellus cochleatus* α-copaene (**92**), δ-cadinene (**30**), α-calacorene (**33**), trans-nerolidol (**5**), cubenol (**41**), epi-cubenol (**42**), fokienol (**8**) and farnesol (**3**) have been identified (Hanssen and Abraham 1986). The acyclic sesquiterpene alcohol E-nerolidol (**5**) was found in *Fistulina hepatica* (Wu et al. 2007) and *Cystoderma carcharias* (Wu et al. 2005). Sesquiterpenes with the sterpurane skeleton were long known only from *Chondrostereum purpureum* and the only volatile compound was the hydrocarbon sterpurene (**111**) (Ayer and Saeedi-Ghomi 1981). Later another source for this type of sesquiterpene was found in a species of the basidiomycotous genus *Gloeophyllum* and 1-hydroxy-3-sterpurene (**112**) was characterized. This alcohol possessed weak antifungal, antibacterial and cytotoxic activities (Rasser et al. 2000).

The hydrocarbon Δ6-protoilludene (**109**) and the related alcohol Δ7-protoilludene-6-ol (**110**) were first found in *Fomitopsis insularis* (Nozoe et al. 1977). From *Fomitopsis pinicola* a huge diversity of sesquiterpene hydrocarbons, e. g. α-cubebene (**84**), α-longipinene (**88**), α-ylangene (**93**), α-(**92**) and β-copaene (**94**), 6-protoilludene (**109**), sativene (**100**), longifolene (**113**), α-(**86**) and β-barbatene (**87**), β-caryophyllene (**61**), (E)-β-farnesene (**2**), α-(**24**) and γ-muurolene (**25**), α-(**26**) and γ-amorphene (**27**), γ-(**29**) and δ-cadinene (**30**), trans-calamene (**31**) and β-calacorene (**34**) and the alcohols trans-nerolidol (**5**), 1-epi-cubenol (**42**) and α-cadinol (**46**) have been reported (Rösecke et al. 2000). Although the volatiles had an effect no specific activity on insects for these sesquiterpenes has been found (Fäldt et al. 1999).

In Asia, a variety of dietary products have been used for centuries as popular medicines to prevent or treat different diseases, including fruiting bodies of mushrooms (Wasser 2011). *Inonotus obliquus* (Chaga) is such a medicinal fungus and has been collected and consumed in Asia for centuries. It contains a large variety of bioactive substances, including triterpenes, proteins, polysaccharides, lipids, and phenols, displaying a wide variety of biological activities in humans (Zheng et al. 2010). The dried fruiting bodies are currently offered worldwide in the form of dietary supplements. It has been used to treat migraine, hypertension, arthritis, bronchitis, asthma, gastritis, haemorrhoids, diabetes, hypercholesterolaemia, hepatitis, and cardiovascular problems. The volatiles of this fungus comprise a huge number of sesquiterpenes and cis-α-(**65**) and trans-α-bergamotene (**66**), α-santalene (**99**), β-sesquifenchene (**76**), epi-β-santalene (**69**), photosantalol (**70**), β-elemene (**14**), β-barbatene (**87**), selina-4,11-diene (**51**), β-(**49**) and δ-selinene (**50**), β-calacorene (**34**), guaiazulene (**81**), selin-11-en-4-α-ol (**52**), α- (**20**) and β-bisabolol (**21**), and β-(**53**) and γ-eudesmol (**54**) have been characterized from *Inonotus obliquus* (Ayoub et al. 2009) (Fig. 4).

Volatile sesquiterpenes and their potential for detection of indoor and crop moulds

The formation of volatile sesquiterpenes by many fungi has been applied for the detection of fungal contaminations. Pezizomycotina species are known to produce a wide range of sesquiterpenes. Members of this subphylum are described as crop and indoor moulds, causing every year a substantial economic damage with co-occurring negative impacts on human health. Therefore, they are highlighted in the search for volatile indicators of fungal contaminants (Schnürer et al. 1999; Pasanen et al. 1996; Van Lancker et al. 2008). Advanced sensorial and analytical methods, such as solid-phase microextraction (SPME), lead to an increasing identification of microbial volatile organic compounds (mVOCs) secreted by these fungal species in the past decades. However, since the production of secondary metabolites is very dependent on growth conditions (temperature, pH, humidity, growth substrate, etc.), characteristic mVOCs for one mould species are



α-Selinene (**48**) β-Selinene (**49**) δ-Selinene (**50**) Selina-4,11-diene (**51**) Selin-11-en-4α-ol (**52**)

β-Eudesmol (**53**) γ-Eudesmol (**54**) 2,7-Dimethyl-1-isopropyl-naphthalene (**55**) Drimenol (**56**)

3-Keto-drimenol (**57**) Aristolochene (**58**) Valencene (**59**) Hypodoratoxide (**60**)

Fig. 4 Volatile sesquiterpenes of the selinane, driman and eremophilane type from fungi hard to determine. Interestingly, a relatively high number of emitted sesquiterpenes was found for the important indoor species *Aspergillus versicolor* and are even shown to increase in later stages of growth (Wilkins et al. 2000; Matysik et al. 2008). However, appropriate sesquiterpenes for direct identification of mould species have not been determined yet. But some of these compounds are known to be intermediates in mycotoxin biosynthesis, e.g. trichodiene (**71**) as a precursor of trichothecene mycotoxins or aristolochene (**58**) in the production of PR-toxin (*Penicillium roqueforti*), and therefore they may be even used as volatile marker for toxic fungal metabolites (Desjardins et al. 1993; Jelen et al. 1997; Larsen 1998). A correlation between mycotoxin production and volatile sesquiterpenes was similarly described for the crop contaminant *Aspergillus flavus* and its highly carcinogenic aflatoxin (Zeringue et al. 1993).

Particularly, in the context of indoor moulds and damp building-related illness the potential of volatile compounds to act also directly as allergens and causing respiratory tract irritation in humans is under constant discussion (Nielsen et al. 2007; Pestka et al. 2008). Important indoor mould species (Andersen et al. 2011) mentioned throughout this article are marked in Table 1.

Some ecological functions of volatile fungal sesquiterpenes

Today more than 25,000 terpene structures have been reported (Dictionary Nat Comp 2008) but still very few have been investigated from a functional perspective. Only in recent years the focus shifted more towards the chemical ecology of volatiles (Harborne 2001). The task, however, to elucidate the ecological function of secondary metabolites in nature is not trivial. Meaningful tests require appropriate doses of sesquiterpenes applied to ecologically relevant target organisms in a realistic manner as part of a well-controlled experiment. Regarding volatile sesquiterpenes it is remarkable that many of them are lipophilic compounds. This suggests that their principal targets are cell membranes and their toxicity is caused by the loss of osmotic control (Inoue et al. 2004). Another possibility is that volatile sesquiterpenes facilitate the passage of other toxins through membranes by acting as solvents and synergizing their effects. Volatile sesquiterpenes are both good conveyors of information over distances because they are lipophilic molecules with moderately high vapour pressures and, due to their vast structural variety, they also allow messages to be very specific. Well established is the role of sesquiterpenes in attracting insect pollinators. Gas chromatography in combination with electroantennogram detection has shown for many insects that terpenes are indeed perceived (de Bruyne and Baker 2008). Another characteristic for volatile sesquiterpenes is that not just only one but usually several often related compounds areproduced. Concerning a given species, the production of mixtures may be seen as a way to enhance certain functions. For communication the release of mixtures may result in messages with more specificity both at the level of receiving species and the activation of responses. For sesquiterpenes used in defense, a mixture may help to achieve simultaneous protection against numerous predators, parasites and competitors. Moreover, mixtures also reduce the risk of the development of resistances (Anderson et al. 2010).

The activity of the sesquiterpenes is manifold and many of them display often rather complex interactions. Some of these compounds are interacting between different fungi and fungal strains. The sesquiterpene hydrocarbons α-(**24**) and γ-muurolene (**25**), α-(**28**) and γ-cadinene (**29**), α-(**26**) and γ-amorphene (**27**), and α-(**37**) and γ-bulgarene (**38**) were produced when the mycelia of the two basidiomycetes *Hypholoma fasciculare* and *Resinicium bicolor* interacted but were not formed in *Resinicium bicolor* alone (Hynes et al. 2007).

Some fungi produce volatile organic compounds for defence against enemies. Among other volatiles the ascomycete *Muscodor albus* produces the sesquiterpenes β-selinene (**49**), α-guaiene (**79**), α-bisabolene (**17**), α-cedrene (**96**), caryophyllene (**61**), α-amorphene (**26**), β-chamigrene (**78**), bulnesene (**80**) and valencene (**59**) (Strobel et al. 2001). Collectively the volatiles acted synergistically to kill a broad range of plant- and human-pathogenic fungi and bacteria. However, an artificial mixture consisting only of the sesquiterpene volatiles had some inhibitory effect against the test fungi and bacteria, but was not lethal. For the sesquiterpene hydrocarbon E-β-farnesene (**2**) it has been reported that it acts as an alarm pheromone in aphids (Kunert et al. 2005) and β-farnesene (**2**), β-humulene (**9**), α-(**24**) and

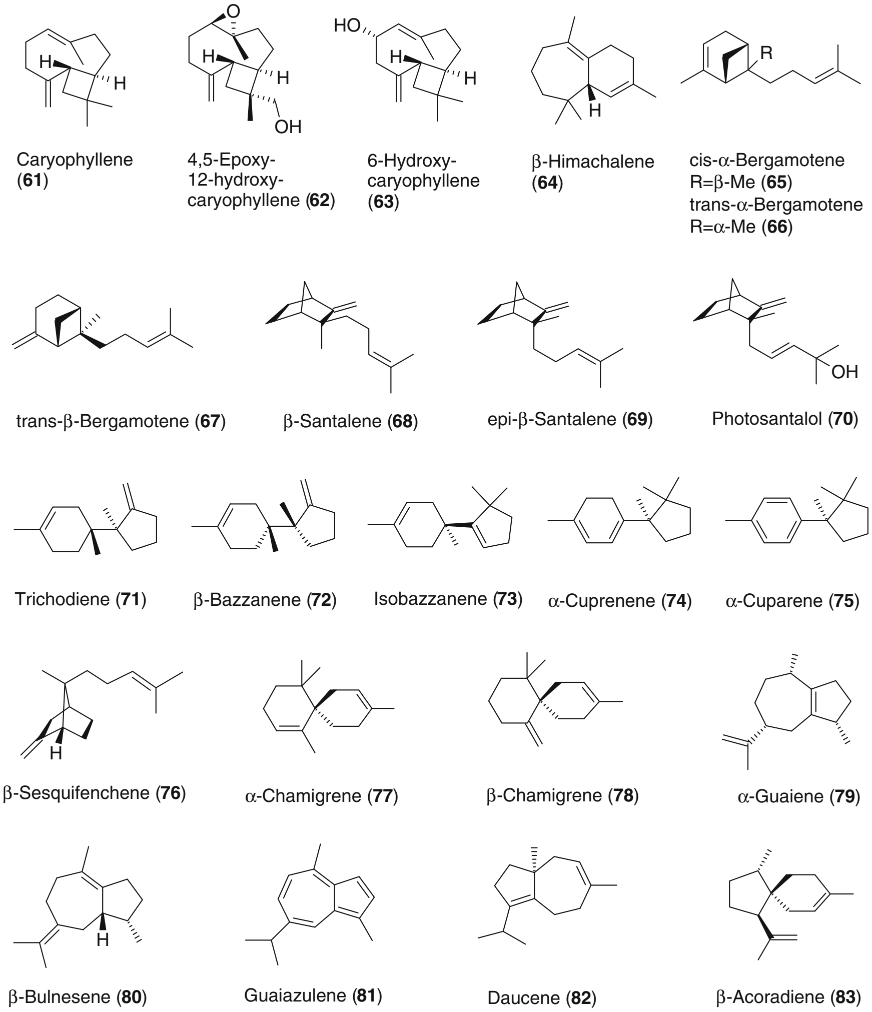


Fig. 5 Other bicyclic volatile sesquiterpenes detected in fungi

γ-muurolene (**25**) act as repellents against herbivores (Halls et al. 1994). For *β*-caryophyllene (**61**) it has been observed that it attracts nematodes which prey on insect larvae (Rasmann et al. 2005) (Fig. 5). From these activities it can be deduced that these compounds have their ecological function in fungi as insect repellents.

The ascomycete (subphylum Pezizomycotina) species *Fusarium oxysporum* is also known to alter growth and morphology of antagonistic fungal strains by the emission of volatile sesquiterpenes. In a plant pathogenic *Fusarium oxysporum* strain, mycelial characteristics and expression of putative virulence factor genes are changed when grown in presence of a non-pathogenic isolate. Only the non-pathogenic strain, which lives in association with a consortium of bacteria, emits the sesquiterpenes α-humulene (**9**) and *β*-caryophyllene (**61**) in larger amounts. Of these α-humulene seems to be responsible for the alterations in the competing pathogenic isolates (Minerdi et al. 2009). In a follow-up study, the same group speculates that *β*-caryophyllene on the other hand might promote growth of lettuce (*Lactuca sativa*). Taken together, non-pathogenic *Fusarium oxysporum* strain and its sesquiterpenes show multitrophic interactions between plants, synergistic organisms and pathogens (Minerdi et al. 2011). After completing this review a study on the production of volatile sesquiterpenes by *Penicillium decumbens* and their ecological functions has been published (Polizzi et al. 2011). The authors detected thujopsene as the main VOC and additionally a huge number of sesquiterpene hydrocarbons, comprising β-farnesene (**2**), β-himachalene (**64**), α-chamigrene (**77**), β-chamigrene (**78**), α-(**74**) and δ-cuprenene, cuparene (**75**), α-, β- (**83**) and 10-epi-β-acoradiene and α-barbatene (**86**). Thujopsene inhibits the growth of five other fungal strains but it also inhibits the growth of the producing *P. decumbens* strain itself. From this finding the authors propose an autorregulatory function of thujopsene.

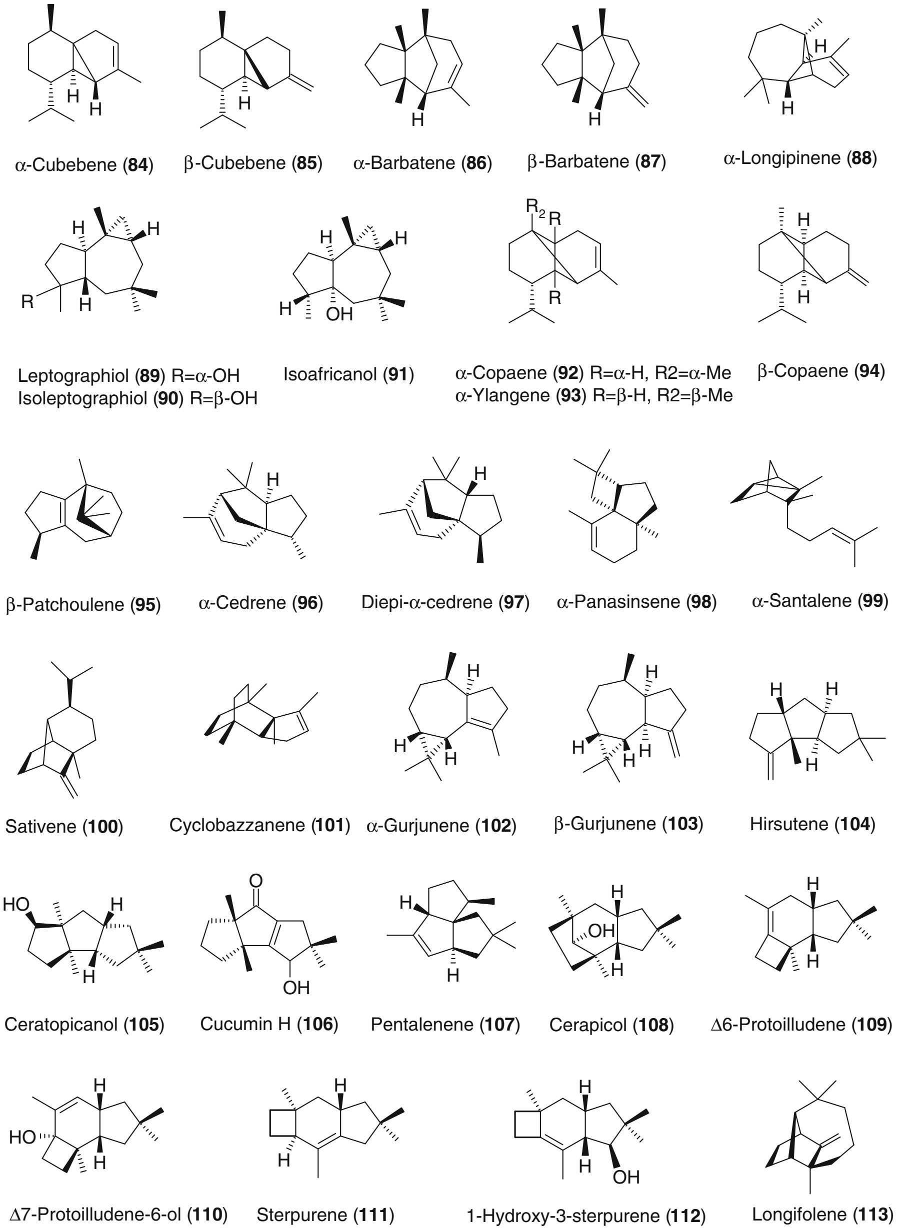
Often the interaction is more complex and produced compounds are further metabolized to the active compounds. The sesquiterpene caryophyllene (**61**) is oxidized by many organisms including fungi (Abraham et al. 1990), plants (Tkachev 1987) and mammals (Asakawa et al. 1986) to the epoxide. This epoxide is a repellent against the leafcutting ant, *Atta cephalotes*. Field bioassays of the terpenoid in Costa Rica confirmed this result; leaves of a preferred plant became repellent when treated with caryophyllene epoxide. Repellency of the epoxide was 20 times greater than that of caryophyllene, its sesquiterpene hydrocarbon precursor. Caryophyllene epoxide was also tested for antifungal activity and found to be an extremely potent compound against many fungi (Hubbell et al. 1983).

Only few sesquiterpene alcohols have been reported from fungi, however, for several of them some specific ecological functions are known. From drimenol (**56**) antifungal activity has been reported (Scher et al. 2004). Torreyol (**40**) is a constituent of *Xylobolus frustulatus* (Van Eijk et al. 1984) and *Cortinarius odorifer* (Egli et al. 1988). (+)-Torreyol (**40**) is also produced by species of the genus *Stereum* and an interesting role of torreyol could be demonstrated during pairings between certain combinations of homokaryotic strains. After immigration of non-self nuclei extensive zones of appressed, degenerative mycelium is formed. From this degenerative mycelium aerial, crystalline filaments, up to 35 µm wide and ≥6 cm long, emerge. The filaments are shown to consist of crystalline (+)-torreyol. Similar filaments can be formed by crystallization of (+)-torreyol from organic solvents or by sublimation indicating that torreyol is excreted by the fungal cells. In the degenerate mycelium novel proteins are produced and the combination of nuclear but not mitochondrial DNA from both progenitors was demonstrated (Ainsworth et al. 1990). Another hint for ecological functions of volatile sesquiterpene alcohols produced by fungi comes from their interactions with insects where several of these alcohols can be detected. For cubenol (**41**), 1-epi-cubenol (**42**), and T-muurolol (**39**) it has been shown that they are recognized by the insect pest *Hypsipyla grandella* (Lago et al. 2006). The torreyol has been found in the male wings of the northern blue butterfly, *Lycaeides argyrognomon*, and may act as an insect pheromone (Lundgren and Bergström 1975). Terrestrol is the marking substance of the male bumble bees and it is found in *Lentinus lepideus* and in other fungi including yeasts (Hanssen et al. 1986c). These findings lead to the hypothesis that these alcohols may be used by some fungi to attract insects for the dispersal of spores and transport to new feeding grounds (Fig. 6).

For a number of these alcohols other ecological functions have been demonstrated. At least for T-muurolol (**39**) and α-cadinol (**46**) antifungal activity against the ascomycetous pathogens *Rhizoctonia solani* and *Fusarium oxysporum* has been reported (Chang et al. 2008). Furthermore, T-cadinol (**47**) stimulates the antennae of several insects including the American cockroach (Nishino et al. 1977) and α-cadinol (**46**) is a repellent against termites showing antimite activity (Chang et al. 2001).

Regarding its ecological function, farnesol (**3**) is probably the best investigated terpene. Since Hornby et al. characterized it as a quorum-sensing molecule (QSM) in the human opportunistic pathogen ascomycete *Candida albicans*, various studies about its function and effects on organisms were published and reviewed (Langford et al. 2009; Morales and Hogan 2010). Therefore, farnesol is a good example how fungal species use volatile signal molecules, like sesquiterpenes, as a powerful device to interact (antagonistic or synergistic) with other microbial organisms. Of all *Candida* species mainly *C. albicans* and *C. dubliniensis* are known to produce the acyclic sesquiterpene alcohol (*E*, *E*)-farnesol (**3**) in larger amounts. It is produced independently of its carbon substrate and acts as an autoinducer in this polymorphic fungal species by inhibition of yeast-to-filamentous switch as well as biofilm formation (Hornby et al. 2001; Ramage et al. 2002; Martins et al. 2007). The precise mode of functioning is still unclear but farnesol is known to impact cAMP-mediated pathways and therefore controls morphology by alteration of gene-expression (Davis-Hanna et al. 2008). In a similar way it further regulates oxidative stress response of *C. albicans* (Deveau et al. 2010).

Fig. 6 Tricyclic volatile sesquiterpenes reported from fungi



Farnesol was shown contributing to the increased resistance of *C. albicans* populations after contact to higher levels of reactive oxygen species (ROS) (Westwater et al. 2005). Extracellular ROS are produced by several organisms and, accordingly, effective defending strategies are vitally important for competing fungal species. Additionally, *C. albicans*-secreted farnesol has also a direct effect on other organisms. Corresponding interspecies interactions are especially investigated with the gram-negative bacterium *Pseudomonas aeruginosa*. The *Pseudomonas* quinolone signal (PQS) and related pyocyanin, which is toxic to *C. albicans*, are shown to be significantly reduced in co-cultures. Farnesol leads to decreased transcript levels of the first gene in the PQS biosynthesis and, therefore, directly impacts the gene expression in competing species (Cugini et al. 2007). Interestingly, also the swarming motility of *P. aeruginosa* may be affected by the same pathway (McAlester et al. 2008). Different studies addressed the effect of farnesol on other microorganisms (Brehm-Stecher and Johnson 2003; Jabra-

Rizk et al. 2006). Exposure of the emerging pathogen *Pneumocystis carnii* (Ascomycota; subphylum Taphrinomycotina) to farnesol was recently shown to substantially inhibit its biofilm formation, suggesting similar FVT (free volatile terpene) signalling in *Pneumocystis* spp. (Cushion et al. 2009). Although directly linked experiments (such as co-cultures) are mostly missing, it gives strong suggestions for growth advantages of the sesquiterpene-producing fungal species in this context. But secretion of farnesol by *Candida* is not only affecting competing bacteria, other fungal species are likewise directly influenced. In the filamentous ascomycetous fungus *Aspergillus nidulans* farnesol induces apoptosis and prevent the development of conidiosphores. Moreover, this effect was shown to be also due to volatile transmission of the sesquiterpene alcohol (Semighini et al. 2006). Similar alterations by farnesol in growth and morphology are described in the Ascomycota species *Fusarium graminearum*, *Aspergillus niger* and *Aspergillus fumigatus* (Lorek et al. 2008; Semighini et al. 2008; Dichtl et al. 2010). Dichtl et al. further suggest that farnesol is interfering in the CWI pathway (cell wall integrity) of which many components are conserved within the kingdom fungi and therefore display an advantage in competition for farnesol-producing fungal species.

Hypomyces odoratus is an ascomycete occurring mostly on higher fungi and producing a typical camphorous odour (Kühne et al. 1991). Main constituent of the volatiles is the sesquiterpene ether hypodoratoxide (**60**) possessing an eremophilane carbon skeleton. The biological activity of hypodoratoxide (**60**) was tested in various assays and it turned out that it has not antibiotic activity but is a phytotoxin (Urbasch et al. 1991). This finding fits well with the observation that many eremophilane sesquiterpenes from fungi, e.g. phomenon, phaseolinone or gigantenone are phytotoxins. The production of phytotoxins by fungi may serve several tasks like niche protection against plants or giving access to nitrogen from dead plant materials.

The basidiomycetous genus *Clitocybe* comprises several hundred species and lives saprophytic in woods. *Clitocybe conglobata* is the producer of a number of oxygenated drimenols. One of them, 3-keto-drimenol (**57**), has been shown to exhibit inhibitory activities against two isozymes of 11β-hydroxysteroid dehydrogenases which catalyze the interconversion of active cortisol and inactive cortisone (Xu et al. 2009). The assays were performed on mammalian enzymes and it is not clear if and how these inhibitory functions have an ecological effect.

Species of the Russulaceae (Basidiomycota) developed an interesting defense mechanism. They produce several sesquiterpene alcohols which are esterified with fatty acids. These fatty acid esters exhibit no or only weak antibiotic activities (Sterner et al. 1989). However, when the fruiting body is injured esterases are activated which cleave the ester and release the free alcohols. These products are chemically very reactive, hence toxic on the one hand but instable on the other hand (Sterner et al. 1985). Some of them are volatiles acting as repellents or kairomones (messengers for interspecies communication that just benefit the receiving organisms) (Raudaskoski and Kothe 2010; Bahn et al. 2007). The sesquiterpene esters serve as prodrugs which are activated after injuries demonstrated in the case of *Lactarius subumbonatus*. *Lactarius subumbonatus* Lindgr. (syn. *L. serifluus* DC), common in the woods of Mediterranean Italy, is characterized by a strong, liquorice-like smell. From the fruit bodies of *L. subumbonatus* 6-hydroxycaryophyllene (S)-6-hydroxystearate was isolated (Clericuzio et al. 1999). The toxicity of this metabolite was tested against the brine shrimp *Artemia salina*. While the ester showed almost no activity the corresponding alcohol 6-hydroxy-caryophyllene (**63**) had an LD_{50} of 11 ppm.

Summarizing, a rather complex picture emerges although still very little is known about the ecological roles of volatile sesquiterpenes from fungi. These compounds act in the communication between fungi, insects and plants, put off insects while others are attracted and defend enemies. Due to the rich diversity of compounds produced a rather specific response from others can be achieved.

Conclusion and outlook

Concerning the perspective of volatile sesquiterpenes from fungi we have to keep in mind that the majority of all fungal species have still not been isolated and are therefore unknown to us (Mueller and Schmit 2007). Hawksworth and Rossman estimated there may be as many as 1 million different fungal species, yet only about 100,000 have been described (Hawksworth and Rosman 1987; Vandenkoornhuyse et al. 2002; Gams 2007). It remains to be seen which fraction of the unknown fungi can be isolated and characterized in the laboratory but even now we can expect that they will contribute novel and unique volatile sesquiterpenes.

The further improvement of the sampling techniques will also broaden our knowledge on volatile sesquiterpenes. Enrichment of volatiles onto solid sorbents has become a popular technique for environmental VOCs analysis in the past decades. However, new and innovative methods are emerging and promise new findings in FVT monitoring. Headspace solid phase dynamic-extraction (HS-SPDE), which combines advantages of an adsorbent fibre and high-efficient concentration capability, was already successfully carried out for high performance analysis in wine fermentations by yeast (Malherbe et al. 2009). HS-SPDE is highly reproducible and, compared with HS-SPME, more effective for most applications but also more intricate (Bicchi et al. 2004). Thus, its application fields maintain limited. Upcoming and promising methods are membrane extraction techniques, e.g. MESI (membrane extraction with a sorbent interface). A larger surface area to extraction-phase volume ratio by a thin-layer sorbent trap is shown to increase the efficiency and sensitivity of VOCs extraction (Bruheim et al. 2003). In 2003, a first study described an on-site application of MESI to monitor volatiles emitted by a living organism (Liu et al. 2004). However, since it is an on-line method (sorbent trap acts simultaneously as an injector) field applications require a portable GC or GC-MS. Nevertheless, for movable samples of smaller size MESI/GC-MS displays a simple and useful alternative in VOCs emission analysis (Wang et al. 2002).

The impact of volatile fungal sesquiterpenes on human health issues has to be considered in several ways. Due to their high bioactivity, terpenes, and sesquiterpenes in particular, are generally highlighted in medical drug design (Abraham 2001; Lindequist et al. 2005). Moreover, a better understanding of FVT signalling in opportunistic pathogenic fungi, like *Candida albicans*, may give new insights into their infectivity. To compete with other organisms and promote own survival or growth, these mechanisms are developed in native environments, e.g. the rhizosphere, and play further essential roles in seizing new surfaces, e.g. the human lung. Especially, in polymicrobial infections a deeper knowledge could allow more precise prognoses for the course of disease and for the outcome of therapies. Also in diagnostics volatile sesquiterpenes are of significance. Used as marker molecules for detection of fungal food or indoor contaminants and mycotoxin detection, these compounds could facilitate a more effective monitoring. By means of electronic nose (e-nose) analysis, which is done in quality control of food industries, they offer potential for precise identification of mycotoxinogenic fungi (Karlshøj et al. 2007).

Our understanding of the chemical ecology of fungi will doubtlessly benefit from the increasing knowledge of the effects of volatile sesquiterpenes on insects and plants. Higher sophisticated analytical techniques will enable fascinating insights into the complex and highly balanced fungi-plants-insects interactions. Some reports have also shown that these chemical networks are modulated by bacteria and even viruses as well (Márquez et al. 2007). A deeper understanding of the chemical ecology of volatile sesquiterpenes will certainly open new windows for applications in the fields of plant protection, insect control and many others.

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