1 Bioactive Secondary Metabolites of Basidiomycetes and Its Potential for Agricultural Plant Growth Promotion

Irina Sidorova and Elena Voronina

1.1 Introduction

Fungi are a major source of bioactive natural compounds with high chemical structure diversity. Tens of thousands of natural products are derived from fungi for medicinal, nutritional, agricultural, and industrial application (Bérdy 2012; Keswani et al. 2014). The ability to produce secondary metabolites (SM) is essential for the most of fungi, but a comparative small number of commonly applied in biotechnology producers may reflect not the highest activity, but rather the large-scale culture simplicity. Further progress in screening for novel compounds and novel producers is necessary in the light of both target organisms acquired resistance and the perspective of the more effective and lesser expensive treatment recognizing (Keswani 2015; Singh et al. 2016).

The sustainable agriculture is a hot spot of modern biology for environmental hazard created by agrochemicals is well-known. The role of fungi in plant growth promotion encompasses nutrient facilitation, plant pathogen and pest biocontrol, and many other effects discussed in a number of current reviews (Mishra et al. 2015; Singh et al. 2017; Varma et al. 2017). Fungal bioactive SMs contribute to plant fitness prominently, thus having a strong agricultural potential (Loiseleur 2017), but different fungal groups are studied in this field rather irregularly.

Fungal class *Agaricomycetes* of *Basidiomycota* phylum (Hibbett et al. 2014), further addressed as basidiomycetes, or basidial fungi, represents a source for perspective novel producers and novel compounds evidently underestimated in agriculture. Wide array of bioactive SM derived from basidiomycetes will be discussed below with focus on its agricultural applications. Some metabolites considered as primary (e.g., fatty acids) with particular SM properties will be mentioned too.

I. Sidorova · E. Voronina (✉)
Lomonosov Moscow State University, Moscow, Russia

H. B. Singh et al. (eds.), *Secondary Metabolites of Plant Growth Promoting Rhizomicroorganisms*, https://doi.org/10.1007/978-981-13-5862-3_1

1.2 Bioactive Secondary Metabolites of Basidiomycetes: An Overview

In the environment basidial fungi meet a number of foes and competitors. Basidiomycete mycelia inhabit the soil, litter, and wood and are able to occupy a range of different substrates existing in multicomponent communities, often under the press of nutrient limitation. Multiple groups of living organisms, such as fungicolous fungi and bacteria, fungivorous insects, mites, nematodes, and others, feed upon basidiomycetes. Over the many million year-long history, basidial fungi have evolved protective mechanisms including chemical defense. Bioactive SMs act as a weapon against competing organisms, occupying and consuming the same substrate, and as signal molecules for inter- and intraspecies communication (Spiteller 2008). These crucial functions facilitated SM production by both basidiomycete fruit bodies and mycelia. A number of SM possess a strong potential for medicine and sustainable agriculture, and some compounds are already exploited at global scale.

1.2.1 The Brief Historical Background

Basidiomycete bioactive SMs were regularly studied since the 1940s. The research was initiated by the mycology laboratories in New York and Oxford. By the early 1950s, about 2000 basidiomycete species were explored, and many of them proved to be active against bacteria and/or fungi; the results are summarized in Florey et al. (1949). Two perspective compounds were detected: pleuromutilin from *Clitopilus scyphoides* and *C. passeckerianus* active against Gram-positive bacteria, further incorporated in veterinary and, later, human therapy (Kavanagh et al. 1951; Novak and Shlaes 2010), and antifungal biformin from *Trichaptum biforme*, the first of basidiomycete polyacetylenes discovered (Zjawiony 2004).

In the 1950s the bioactive compound screening switched to actinomycetes as producers of novel promising antibiotics (streptomycin, chloramphenicol, tetracyclines, polyenes), thus retarding studies in the field of fungi (Bérdy 2005). However there was a revival of scientific interest toward basidiomycete active compounds, and the numbers given below can rather expressively indicate that. Only 300 basidiomycete antibiotics (23% of all fungi-derived) were revealed in 1940–1974, but in 1975–2000 its number grew up to 1500 (46%) and in 2001–2010 – to 1800 (61%) (Bérdy 2012). Undoubtedly, this “basidiomycete boom” was induced by many advances in medicinal fungi, the group embracing mostly basidial ones (De Silva et al. 2013; Chen and Liu 2017; Gargano et al. 2017).

Antifungal natural β-methoxyacrylic acid derivatives, strobilurins and oudemansins, produced by different basidiomycetes were originally isolated from *Strobilurus tenacellus* (Anke et al. 1977). These SMs became lead compounds for chemical synthesis of widely applied agricultural and industrial fungicides (Clough 2000). The achievements of basidiomycete bioactive SM research are reviewed in Anke

(1989), Lorenzen and Anke (1998), Schüffler and Anke (2009), De Silva et al. (2013), and Chen and Liu (2017).

1.2.2 Chemical Structure of Basidiomycete Bioactive Compounds and Producing Species

There are about 90,000 natural bioactive metabolites known by present; 15,600 (nearly 17%) are fungi-derived. Fungi are the champions among all microorganisms producing 45.8% of all microbial-derived SM. Basidiomycetes' contribution is notable, namely, 3600 (23%) high diverse bioactive compounds (Bérdy 2012). The most comprehensive recent review on the topic is authored by Chen and Liu (2017).

Contrary to primary metabolites, SMs are individually produced compounds, often specific for a single species or a limited species group (Turner and Aldridge 1983). By the way, polyacetylenes in fungi are detected only in some basidiomycetes (Hanson 2008). At the same time, some SMs are produced by members of different families or even orders (Table 1.1). Besides, SM diversity is enlarged by multiple chemical derivatives produced by the same species or a number of related ones. The modifications differ in some functional groups, activity, and other traits. Some examples are β-methoxyacrylate derivatives such as strobilurins A–F; oudemansins A, B, and X; 9-methoxystrobilurin K and L; etc. (Zakharychev and Kovalenko 1998) and numerous sesquiterpenoids of *Granulobasidium vellereum*, viz., illudane, illudalane, and protoilludane (Kokubun et al. 2016).

Carbon backbone in SM consists from glucose-derived C entering the biosynthesis via several routes. Despite enormous diversity, SMs are created through a rather few biogenetic pathways (Turner and Aldridge 1983). The similar in its early steps polyketide synthesis and fatty acids and terpene synthesis involves acetyl-CoA. Other biogenetic pathways, not based on acetate, include nonribosomal peptide synthesis and shikimate pathway. Contrary to plant and actinomycete compounds, the incorporation of intact glucose C backbone is very rare in fungal SM. Some compounds are derived from amino acids, through trioses and pyruvate, or through shikimic acid.

Terpene biosynthesis is the most important SM pathway in fungi and plants (Turner and Aldridge 1983). Terpene chemical structure is derived from isoprene C5 units linked together "head to tail." Isopentenyl pyrophosphate, the original chemical unit, derives from acetate through mevalonate. Isopentenyl pyrophosphate and its derivative dimethylallyl pyrophosphate condensation results in creation of different terpenes. According to C numbers per molecule, basidiomycete terpenes are classified into monoterpenes (C10), sesquiterpenes (C15), diterpenes (C20), sesterterpenes (C25), triterpenes, and steroids (C30). Basidial fungi produce a range of different terpenoids – terpenes containing additional functional groups – and the sesquiterpenoids are the most abundant. These SMs are distributed in nearly all basidiomycete orders examined (Hanson 2008; Schmidt-Dannert 2014). One of the most promising diterpenoids is antibacterial pleuromutilin (Kavanagh et al. 1951; Schǖffler and Anke 2014). Triterpenoids are scarce in basidiomycetes, but

Table 1.1 Secondary metabolites with antifungal activities detected in basidiomycetes

Groups of chemical compounds	Bioactive secondary metabolites	Producer fungal species[a]	Producer species position in taxonomy (family, order)[a]	References
Terpenoids	Enokipodins A–D	*Flammulina velutipes* (Curtis) Singer	*Physalacriaceae*, *Agaricales*	Ishikawa et al. (2001)
Sesquiterpenoids	1(10),4-Germacradiene-2,6,12-triol	*Hohenbuehelia leightonii* (Berk.) Watling ex Courtec. et Roux	*Pleurotaceae*, *Agaricales*	Eilbert et al. (2000)
	Hyphodontal	*Hyphodontia* sp.	*Schizoporaceae*, *Hymenochaetales*	Erkel et al. (1994)
	Hyphodontal	*Mycoacia uda* (Fr.) Donk	*Meruliaceae*, *Polyporales*	Schüffler et al. (2012)
	Marasmene B, marasmals B, C	*Marasmius* sp.	*Marasmiaceae*, *Agaricales*	Liermann et al. (2012)
	Melleolides	*Armillaria mellea* (Vahl.) P.Kumm.	*Physalacriaceae*, *Agaricales*	Bohnert et al. (2014)
	Nebularic acids A, B, nebularilactones A, D	*Clitocybe nebularis* (Batsch) P.Kumm.	*Tricholomataceae*, *Agaricales*	Wangun et al. (2006)
	Penarines A–F	*Hygrophorus penarius* Fr.	*Hygrophoraceae*, *Agaricales*	Otto et al. (2014)
	Rufuslactone	*Lactarius rufus* (Scop.) Fr.	*Russulaceae*, *Russulales*	Luo et al. (2005b)
	Sterelactones	*Stereum* sp.	*Stereaceae*, *Russulales*	Opatz et al. (2008)
	Udalactaranes A, B	*Mycoacia uda* (Fr.) Donk	*Meruliaceae*, *Polyporales*	Schüffler et al. (2012)
Diterpenoids	Heptemerones A–G	*Coprinellus heptemerus* (M. Lange et A.H. Sm.) Vilgalys, Hopple et Jacq. Johnson	*Psathyrellaceae*, *Agaricales*	Kettering et al. (2005)
	Herical	*Hericium coralloides* (Scop.)Pers., *H. abietis* (Weir ex Hubert) K.A. Harrison	*Hericiaceae*, *Russulales*	Anke et al. (2002)
	Scabronines G, H	*Sarcodon scabrosus* (Fr.) P. Karst.	*Bankeraceae*, *Thelephorales*	Ma et al. (2010)
	Tintinnadiol	*Mycena tintinnabulum* (Paulet) Quél.	*Mycenaceae*, *Agaricales*	Engler et al. (1998b)
Sesterterpenoids	Aleurodiscal	*Aleurodiscus mirabilis* (Berk. et M.A.Curtis) Parmasto	*Stereaceae*, *Russulales*	Lauer et al. (1989)

Groups of chemical compounds	Bioactive secondary metabolites	Producer fungal species[a]	Producer species position in taxonomy (family, order)[a]	References
Triterpenoids	Favolon	*Favolaschia calocera* R. Heim, *Favolaschia* sp.	*Mycenaceae*, *Agaricales*	Anke et al. (1995), Chepkirui et al. (2016)
	Favolon B	*Mycena* sp.	*Mycenaceae*, *Agaricales*	Aqueveque et al. (2005)
Steroids	Laschiatrion	*Favolaschia* sp.	*Mycenaceae*, *Agaricales*	Anke et al. (2004)
Alkenes	Scorodonin	*Mycetinis scorodonius* (Fr.) A.W.Wilson et Desjardin	*Omphalotaceae*, *Agaricales*	Anke et al. (1980)
Polyacetylenes	Biformin	*Trichaptum biforme* (Fr.) Ryvarden	*Incertae sedis*, *Hymenochaetales*	Zjawiony (2004)
	1-Hydroxy-2-nonin-4-on	*Ischnoderma benzoinum* (Wahlenb.) P. Karst.	*Fomitopsidaceae*, *Polyporales*	Anke et al. (1982)
Prenylphenols	Grifolin	*Polypus dispansus* (Lloyd) Audet	*Incertae sedis*, *Russulales*	Luo et al. (2005a)
Benzoquinone derivatives	Mycenon	*Mycena* sp.	*Mycenaceae*, *Agaricales*	Hautzel et al. (1990)
Isocoumarin derivatives	Gymnopalynes A, B	*Gymnopus* sp.	*Omphalotaceae*, *Agaricales*	Thongbai et al. (2013)
Cyclopentenone derivatives	Hygrophorones A–G	*Hygrophorus* spp.	*Hygrophoraceae*, *Agaricales*	Lübken et al. (2004)

(continued)

Table 1.1 (continued)

Groups of chemical compounds	Bioactive secondary metabolites	Producer fungal species[a]	Producer species position in taxonomy (family, order)[a]	References
Methoxyacrylate derivatives	Oudemansin	*Mucidula mucida* (Schrad.) Pat.	*Physalacriaceae*, *Agaricales*	Anke et al. (1979)
	Oudemansin A	*Gymnopus vernus* (Ryman) Antonín et Noordel.	*Omphalotaceae*, *Agaricales*	Engler et al. (1998a)
	Oudemansin X	*Hymenopellis radicata* (Relhan) R.H. Petersen	*Physalacriaceae*, *Agaricales*	Anke et al. (1990)
	9-Oxostrobilurins A, G, K, and I	*Favolaschia calocera* R. Heim	*Mycenaceae*, *Agaricales*	Chepkirui et al. (2016)
	Strobilurins	*Gymnopus vernus* (Ryman) Antonín et Noordel.	*Omphalotaceae*, *Agaricales*	Engler et al. (1998a)
	Strobilurins	*Strobilurus tenacellus* (Pers.) Singer	*Physalacriaceae*, *Agaricales*	Anke et al. (1977)
Peptides	Alveolarin	*Neofavolus alveolaris* (DC.) Sotome et T. Hatt.	*Polyporaceae*, *Polyporales*	Wang and Ng (2004b)
	Eryngin	*Pleurotus eryngii* (DC.) Quél.	*Pleurotaceae*, *Agaricales*	Wang and Ng (2004a)
	Pleurostrin	*Pleurotus ostreatus* (Jacq.) P. Kumm.	*Pleurotaceae*, *Agaricales*	Chu et al. (2005)

[a] The fungal species names and their position in taxonomy are provided according to the Index Fungorum database (http://www.indexfungorum.org/, accessed on 2018/01/28)

antifungals favolons were detected in *Favolaschia* and *Mycena* species (Anke et al. 1995; Aqueveque et al. 2005) (Table 1.1).

Polyketide and fatty acid metabolic routes are homologous both in the process of chain elongation via the common pool of simple precursors and in the synthases' types (Turner and Aldridge 1983). Polyketides derive from repetitive decarboxylative condensation of the primer (acetyl-CoA) with several units of malonyl-CoA. The products created are instable and stabilize by aromatization with one or several ring buildings. Polyketide formation is arranged by polyfunctional enzymes, polyketide synthases (PKS). Basidiomycete polyketides include antifungals isolated from *Hygrophorus* species – hygrophorones (Lūbken et al. 2004) and chrysotriones (Gilardoni et al. 2007) and numerous methoxyacrylate derivatives (Clough 1993). The fatty acid biosynthesis differs in reduction accompanying repetitive condensation of acetyl-CoA with malonyl-CoA through the action of acyl carrier protein. Basidiomycetes are rich in fatty acids and their derivatives, in particular, bioactive ones (Stadler et al. 1994b). Polyacetylenes – linear compounds with double or triple conjugated bonds – are fatty acid derivatives known only from higher plants and basidial fungi (Hanson 2008). Thorough examination of 300 basidiomycete species revealed that 10% of them are able to produce significant amounts of polyacetylenes under culture conditions. Many compounds demonstrated biological activity, such as the first discovered biformin (Zjawiony 2004).

The lesser significant for fungal secondary metabolism shikimate pathway starts with the condensation of phosphoenolpyruvate and erythrose-4-phosphate. These precursors are derived from glucose conversion via glycolysis and pentose phosphate pathway. Further metabolic route involves shikimate and chorismate. This pathway is typical for plants and fungi, but is absent in animals (Hanson 2008). Basidiomycete SMs derived from it include terphenyls of *Thelephora* spp. and *Sarcodon* spp. (*Thelephoraceae*) (Schüffler and Anke 2009) and pulvinic acids of *Boletales* (Turner and Aldridge 1983).

The last but not least SM pathway is nonribosomal peptide synthesis (Finking and Marachiel 2004). Nonribosomal peptides are originated through the action of specialized nonribosomal peptide synthetases (NPRS) consisting of a series of functional units. They are able to bind amino acids, to activate them in the form of thioesters, and to join them to elongated peptide chain. This way results in a colossal diversity of peptides derived. Ribosomal synthesis allows operation with standard array of *L*-amino acids only, but nonribosomal peptides can contain unusual structural units, such as non-proteinogenic amino acids (*D*-isomers) and standard amino acids modified by methylation, hydroxylation, and glycosylation. The research of basidiomycete bioactive peptides was initiated later than of other SM groups. Nematicidal cyclic dodecapeptide omphalotin was the first revealed (Mayer et al. 1997). By present several effective antifungal peptides have been discovered, including eryngin (Wang and Ng 2004a), alveolarin (Wang and Ng 2004b), and pleurostrin (Chu et al. 2005).

Nearly all basidiomycete taxa produce bioactive SM, but producing species numbers are distributed unevenly for several reasons. A range of species, especially, symbiotrophs, are recalcitrant to isolation and management in axenic culture, thus impeding their involvement into biotechnology processes. Many fungal groups were examined for SM only at the fruitbody stages with mycelial phase remained totally unexplored. Basidiomycetes are an extremely large group, and biological activity was examined in relatively small proportion of species. Regular fungal surveys are only starting in many regions, and one can expect new undescribed species detection. Moreover, the system of *Basidiomycota* recently underwent drastic changes (Hibbett et al. 2014), thus giving rise to misinterpretation of identity and taxonomy position of SM-producing species studied in the previous years.

However, the analysis of bioactive SM producer distribution within taxa is a promising challenge both for novel compound screening and basidiomycete chemotaxonomy investigation. Ranadive et al. (2013) analyzed data on antibacterial and antifungal activity of 281 basidiomycete species of 122 genera and 45 families and tried to rank these taxa according to detected producers' numbers. Family *Polyporaceae* (64 species active) was in lead; a "bad second" and so on were *Agaricaceae*, *Hymenochaetaceae*, and *Tricholomataceae* (22, 21, and 16 species, respectively). Unfortunately, the sample analyzed was quite small compared to known number of bioactive SMs – 3600 (Bérdy 2012). In addition, families compared are sharply unequal in their volume, and for future screening, plotting this ranking is disadvantageous for perspective species from small families. A similar research concerned analysis of bioactive compounds' producers from all groups of biota assembled as a tree of life (Zhu et al. 2011). Here basidiomycetes obtained rather lowly position, but orders *Agaricales* and *Polyporales* were pointed out as promising groups. So, "the size matters" again: the larger taxa got the more privileges without any attention to taxonomic divisions (here, the families). The examples given demonstrate the perspectives of bioactive SM producers' taxonomic analysis for novel compound screening, but this approach requires activity target detailing, representative samples of species arranging, and standardization of taxonomic structure within the sample.

1.2.3 Biological Activity of Basidiomycete Secondary Metabolites

Reviewing the complete array of basidiomycete chemical potential is beyond the scope of this chapter. For it is aimed to discuss basidial fungi perspectives in agriculture, the SMs outlined below are either antifungals (in particular, inhibiting plant pathogenic fungi) or nematicidal, insecticidal, and acaricidal compounds affecting plant pests.

However, discussing the bioactivity, it is necessary to mention the antibacterial pleuromutilin illustrating biotechnological and bioengineering potential of basidial SMs. The tricyclic diterpene was originally isolated from the cultures of *Clitopilus scyphoides* and *C. passeckerianus*, and its natural derivatives were detected too (Kavanagh et al. 1951; Knauseder and Brandl 1976; Hartley et al. 2009). The antibiotic is a protein synthesis inhibitor active against Gram-positive bacteria, including methicillin-resistant staphylococci and mycoplasmas (Poulsen et al.

2001). Semisynthetic analogues were implicated in veterinary since 1979 (tiamulin) and entered human medicine in 2007 (retapamulin) as a treatment for superficial skin infections caused by *Staphylococcus aureus* and *Streptococcus pyogenes* (Daum et al. 2007). Novel pleuromutilin analogues were synthesized for wider medicinal application (Yang and Kean 2008; Tang et al. 2012). All the enzymes contributing to pleuromutilin biosynthesis were characterized, the metabolic pathway was proposed, and the cluster of seven genes operating the process was identified. The biotransformation was carried out in the heterologous host (*Aspergillus oryzae*), thus allowing 2106% increase in the antibiotic production (Bailey et al. 2016; Yamane et al. 2017). These achievements can surely encourage the researchers in the laborious work with basidiomycete SM-producing species.

Various antifungal SMs derived from basidiomycetes are summarized in Table 1.1. It should be noted that activity was often revealed in preliminary experiments, while the main goal was the chemical structure recognition. Terpenoids, mainly sesquiterpene derivatives, are produced by diverse fungal taxa with a slight predominance of some *Agaricales* families. Melleolides, protoilludene alcohols esterified with orsellinic acid, proved to be both active against micromycetes (activity is based on the double bond in the protoilludene moiety) and cytotoxic compounds. It is noteworthy that antifungal melleolides interfere with metabolite-related gene transcription in their targets (Bohnert et al. 2014). Sesquiterpenoids recognized by present are not antifungals only, but can affect nematodes, mites, and multiple insects, in the latter case exhibiting both insecticidal and deterrent activities. Cheimonophyllons A–E and cheimonophyllal, bisabolane-type sesquiterpenoids, isolated from *Cheimonophyllum candidissimum*, showed weak antifungal and antibacterial activities, but were toxic for nematodes (Stadler et al. 1994a) (Table 1.2). Granulolactone and granulodione (derivatives from illudalane and 15-norilludane, respectively) isolated from *Granulobasidium vellereum* exhibit acaricidal and insecticidal activities (Kokubun et al. 2016). Some basidiomycete sesquiterpenoids are known as direct plant growth promoters. Protoilludene sesquiterpenes from *Lactarius repraesentaneus*, repraesentins A–C, stimulated radicle elongation in the lettuce seedlings (Hirota et al. 2003).

Diterpenoides scabronines G and H have an ability to affect in low concentrations plant pathogenic fungi and, to a lesser extent, bacteria (Ma et al. 2010). *Mycena tintinnabulum* growing on the nutritional medium and on wood possesses a complex of antifungals, comprising strobilurins and a new diterpenoid tintinnadiol. The latter was detected only in fruit bodies and exhibited cytotoxicity (Engler et al. 1998b). Diterpenoides heptemerones A–G were derived from *Coprinellus heptemerus* culture while screening for antagonists to deleterious rice pathogen *Magnaporthe grisea*. These compounds inhibited pathogen spore germination, but not affected the mycelial growth. Four heptemerones showed plant protective activity against pyriculariosis in the experiment with leaf segments. SM had a wide range of action, inhibiting yeasts and bacterial growth and demonstrating a strong cytotoxical effect. Phytotoxicity, however, was detected for heptemerone D only (Kettering et al. 2005).

Antifungal sesterterpenoids are rare within basidiomycetes. Aleurodiscal derived from *Aleurodiscus mirabilis* causes abnormal apical branching in *Mucor miehei* hyphae in very low concentrations (Lauer et al. 1989) (Table 1.1). Chrysotriones A and B, 2-acylcyclopentene-1,3-dione derivatives, were detected in *Hygrophorus chrysodon* fruit bodies (Gilardoni et al. 2007). Preliminary data pointed at activity against widespread plant pathogen *Fusarium verticillioides*. Chrysotriones were suggested to protect their producer's fruit bodies against fungicolous fungi. Antifungal *β*-methoxyacrylic acid derivatives, strobilurins and oudemansins, are basidiomycete-derived active compounds most widely applied in agriculture by present and will be discussed in the second subchapter.

Screening for the novel natural nematicidal SM active against *Meloidogyne incognita* revealed the cyclic peptide omphalotin in the mycelium of *Omphalotus olearius*, known as producer of sesquiterpenoids illuidines M and S with high antimicrobial activity and cytotoxicity (Table 1.2). Omphalotin exhibits remarkable, outmatching the commercial ivermectin, activity against the pathogenic nematode *M. incognita*, but affects the saprobic species *Caenorhabditis elegans* far lesser and has no antimicrobial and phytotoxic properties (Mayer et al. 1997). Subsequently four new omphalotin variations (E–I) were revealed and recognized as cyclic dodecapeptides (Liermann et al. 2009). Omphalotins are promising bioactive SMs with highly selective action against nematodes.

Peptides and proteins with molecular weight 7–28 kDa were isolated from fruit bodies of some basidiomycete species (*Pleurotus eryngii*, *P. ostreatus*, *Ganoderma lucidum*, *Neofavolus alveolaris*, etc.). These compounds inhibit plant pathogenic fungi *Botrytis cinerea*, *Fusarium oxysporum*, *Mycosphaerella arachidicola*, and *Physalospora pyricola* growth by mechanism not elucidated yet (Wang and Ng 2004a, b, 2006; Chu et al. 2005). Protease-inhibiting proteins were detected in *Clitocybe nebularis* (Avanzo et al. 2009), *Macrolepiota procera* (Sabotič et al. 2009), and some other species. These SMs act both as regulators and protectors; insecticidal activity of cnispin against the model dipteran *Drosophila melanogaster* was demonstrated (Avanzo et al. 2009). The current opinion on fungal toxic proteins, e.g., mycospin and mycocypin families, and perspectives of their research and agricultural application are outlined in Sabotič et al. (2016).

1.3 Potential and Application of Basidiomycete Bioactive Secondary Metabolites for Agricultural Plant Growth Promotion

Different aspects of sustainable agriculture are now in the focus of research because of a global urgent need to create an alternative for toxic, expensive, and ecologically non-friendly agrochemicals. It is widely acknowledged that even registered commercial "-cides" have multiple side effects and can be harmful for nontarget beneficial living organisms. Thus biocontrol method implying natural or closely related synthetic bioactive compounds for plant growth promotion could be considered far more preferable. Various organisms can contribute in many ways to plant growth promotion, and the most popular and well recognized are bacteria, particularly rhizobial and soil-borne microfungi, predominantly of ascomycete

Table 1.2 Secondary metabolites with nematicidal activities detected in basidiomycetes

Groups of chemical compounds	Bioactive compounds	Producer fungal species[a]	Producer species position in taxonomy (family, order)[a]
Terpenoids	Illinitone A	*Limacella illinita* (Fr.) Maire	*Amanitaceae*, *Agaricales*
Monoterpenes	1,2-Dihydroxymintlactone	*Cheimonophyllum candidissimum* (Sacc.) Singer	*Cyphellaceae*, *Agaricales*
Sesquiterpenes and derivatives	Cheimonophyllal cheimonophyllons A, B, C, D, and E	*Cheimonophyllum candidissimum* (Sacc.) Singer	*Cyphellaceae*, *Agaricales*
	Cheimonophyllon E	*Pleurotus eryngii* (DC.) Quél.	*Pleurotaceae*, *Agaricales*
	2β,13-Dihydroxyledol	*Dichomitus squalens* (P. Karst.) D.A. Reid	*Polyporaceae*, *Polyporales*
	Isovelleral	*Lactarius vellereus* (Fr.) Fr.	*Russulaceae*, *Russulales*
	Isovelleral	*Russula cuprea* J.E. Lange	*Russulaceae*, *Russulales*
	Lactarorufins A and B, furantriol	*Lactarius aurantiacus* (Pers.) Gray	*Russulaceae*, *Russulales*
	Marasmic acid	*Lachnella villosa* (Pers.) Donk, *Lachnella* sp. 541	*Niaceae*, *Agaricales*
	Marasmic acid	*Strobilurus conigenus* (Pers.) Gulden	*Physalacriaceae*, *Agaricales*
	Marasmic acid	*Peniophora laeta* (Fr.) Donk	*Peniophoraceae*, *Russulales*
	Stereumins A, B, C, D, and E	*Stereum* sp. CCTCC AF 207024	*Stereaceae*, *Russulales*
Simple aromatic compounds	*p*-Anisaldehyde, *p*-anisyl alcohol, 1-(4-methoxyphenyl)-1,2-propanediol, 2-hydroxy-(4′-methoxy)-propiophenone	*Pleurotus pulmonarius* (Fr.) Quél.	*Pleurotaceae*, *Agaricales*
	3,5-Dihydroxy-4-(3-methyl-but-2-enyl)-benzene-1,2-dicarbaldehyde, butyl 2,4-dihydroxy-6-methylbenzoate	*Stereum* sp. 8954	*Stereaceae*, *Russulales*
	Methyl 3-*p*-anisoloxypropionate	*Irpex lacteus* (Fr.) Fr.	*Meruliaceae*, *Polyporales*

(continued)

Table 1.2 (continued)

Groups of chemical compounds	Bioactive compounds	Producer fungal species[a]	Producer species position in taxonomy (family, order)[a]
O-containing heterocyclic compounds	4,6-Fimethoxyisobenzofuran-1(3*H*)-one, 5-methylfuran-3-carboxylic acid, 5-hydroxy-3,5-dimethylfuran-2(5*H*)-one, 4,6-dihydroxybenzofuran-3(2*H*)-one, 5-hydroxy-3-(hydroxymethyl)-5-methylfuran-2(5H)-one, 4,6-dihydroxyisobenzofuran-1,3-dione, 3-formyl-2,5-dihydroxybenzylacetate	*Coprinus comatus* (O.F. Müll.) Pers	*Agaricaceae*, *Agaricales*
	7,8,11-Drimanetriol	*Coprinellus xanthothrix* (Romagn.) Vilgalys, Hopple et Jacq. Johnson	*Psathyrellaceae*, *Agaricales*
	5-Hydroxymethyl-furancarbaldehyde	*Pleurotus eryngii* (DC.) Quél.	*Pleurotaceae*, *Agaricales*
	5-Pentyl-2-furaldehyde, 5-(4-pentenyl)-2-furaldehyde	*Irpex lacteus* (Fr.) Fr.	*Meruliaceae*, *Polyporales*
Benzoquinone derivatives	Mycenon	*Mycena* sp.	*Mycenaceae*, *Agaricales*
N-containing heterocyclic compounds	Xanthothone, 2-(1H-pyrrol-1-yl)-ethanol	*Coprinellus xanthothrix* (Romagn.) Vilgalys, Hopple et Jacq. Johnson	*Psathyrellaceae*, *Agaricales*
Alkaloids	2-Aminoquinoline	*Leucopaxillus albissimus* (Peck) Singer	*Tricholomataceae*, *Agaricales*
	Phenoxazone	*Calocybe gambosa* (Fr.) Donk	*Lyophyllaceae*, *Agaricales*
	Phenoxazone	*Pycnoporus sanguineus* (L.) Murrill	*Polyporaceae*, *Polyporales*
Alkynes	2,4,6-Triacetylenic octane diacid	*Wolfiporia cocos* (F.A. Wolf) Ryvarden and Gilb.	*Polyporaceae*, *Polyporales*

(continued)

Table 1.2 (continued)

Groups of chemical compounds	Bioactive compounds	Producer fungal species[a]	Producer species position in taxonomy (family, order)[a]
Fatty acids[b]	*Trans*-2-decenedioic acid	*Pleurotus ostreatus* (Jacq.) P. Kumm.	*Pleurotaceae*, *Agaricales*
	S-coriolic acid, linoleic acid	*Pleurotus pulmonarius* (Fr.) Quél.	*Pleurotaceae*, *Agaricales*
	Linoleic acid, oleic acid, palmitic acid	*Hericium coralloides* (Scop.) Pers.	*Hericiaceae*, *Russulales*
Peptides	Beauvericin	*Laetiporus sulphureus* (Bull.) Murrill	*Fomitopsidaceae*, *Polyporales*
	Omphalotins A, B, C, and D	*Omphalotus olearius* (DC.) Singer	*Omphalotaceae*, *Agaricales*
	Phalloidin	*Conocybe apala* (Fr.) Arnolds	*Bolbitiaceae*, *Agaricales*

Modified from Li and Zhang (2014), references to the original research see in Li and Zhang (2014), Askary and Martinelli (2015)

[a] The fungal species names and their position in taxonomy are provided according to the Index Fungorum database (http://www.indexfungorum.org/, accessed on 2018/01/28)

[b] Fatty acids are traditionally ascribed to primary metabolites, but the compounds outlined here exhibit traits essential for secondary metabolism

affinity (Singh et al. 2017). Basidiomycetes didn't get much attention from the researchers because of the range of obstacles interfere their exploration and application, but there are evidences for the encouraging progress in their SM research both with examples of successful implication in agriculture and industry.

1.3.1 Strobilurins, Oudemansins, and Their Derivatives as Biopesticides Protective Against Plant Pathogens

Fungi play an important role in the agriculture as a rich source of plant defensive bioactive compounds. They can be applied as a base for commercial preparations, but more often they act as leads for structural modifications aimed at increasing or changing their activities and target group resistance reduction. Such products share advantages both from biotechnology and chemistry approaches (Loiseleur 2017).

The route "from mushroom to molecule to market" was successfully marched by strobilurin fungicides derived from basidiomycete bioactive SMs (Clough 2000; Balba 2007). The first active compound from this group, strobilurin A, was isolated in 1977 in Germany from *Strobilurus tenacellus* (Anke et al. 1977). Lately oudemansin was generated in the same laboratory (Anke et al. 1979). The compounds possessed high and selective antifungal activity along with low toxicity and no antibacterial effects. Their chemical structure was rather uncommon for basidiomycete SM; the compounds contain methoxyacrylate moiety in the form of methyl ether or amide linked through carbon atom to the rest of the molecule (Clough 1993).

Now plenty of natural strobilurins' variations are recognized, differing in the structure of aliphatic chain and in the presence/position of functional groups. The strobilurins' mode of action was uncommon as well; they inhibit cell respiration, thus disrupting electron transport at complex III in the mitochondrial membrane (Von Jagow et al. 1986).

Strobilurins, oudemansins, and their numerous modifications are produced by several families of basidial fungi. The producers are *Strobilurus*, *Oudemansiella*, *Hydropus*, *Mucidula*, *Merismodes*, *Favolaschia*, *Mycena* spp., and others (Anke 1995). They are common litter or wood dwellers with wide distribution, reported from all continents. Strobilurin production was observed not only at laboratory media but in the natural environment too (Engler et al. 1998a). The compounds considered to provide effective protection for their producers.

Comparatively simple chemical structure, stable high activity despite significant structural variations, principally new mechanism of action implying the absence of cross resistance in pathogens resistant to registered fungicides, and low toxicity of some strobilurin modifications facilitate chemical analogue synthesis. There was another challenge: to obtain photostable compounds without loss of fungicidal activities, for the natural SMs were subject to rapid light degradation. A bulk body of research articles and several reviews describe strobilurin derivative synthesis (Zakharychev and Kovalenko 1998; Clough 2000). The first synthetic strobilurins were introduced to the market in 1996. Soon they ranked with the most asked-for commercial fungicides at global scale (Balba 2007). Azoxystrobin (Syngenta) is one of the most popular. Nearly all the largest world pesticide-producing companies accomplish fundamental research of strobilurins, and over 70,000 compounds of this group are recognized by now. Synthetic analogues of natural compounds are patented as agricultural and industrial fungicides with wide-range activities, as nematicides, insecticides, and acaricides. Redox reactions in cytochrome system are common for many groups of living organisms, so respiration inhibitors are effective against various pests and pathogens. Many synthetic strobilurin analogues are active not only against the fungi but against insects, mites, and nematodes too (Balba 2007).

One of the key points of azoxystrobin's outstanding commercial success is its ability to destroy both ascomycete and basidiomycete fungi along with oomycete pseudofungi. Nearly all strobilurins are highly effective against downy mildews, rust fungi, powdery mildews, and various blights (alternariosis, cercosporosis, etc.). Azoxystrobin is able to inhibit such co-occurring plant pathogen groups (e.g., downy and powdery mildews of grapevine), which previously required a complex treatment including two or more fungicides. Another significant advantage is strobilurins' high activity against a complex of plant pathogens specialized for a range of crops. By the way, there are compounds with narrow-ranged activity, e.g., for the rice treatment only.

1.3.2 Bioactive Metabolites of Ectomycorrhizal Fungi and Its Potential in Sustainable Agriculture

Mycorrhiza is a widely acknowledged beneficial plant-fungus symbiosis, so mycorrhizal fungi represent in many ways promising guild for sustainable agriculture and forestry. There is a large body of literature concerning the multifaceted role of mycorrhiza in plant growth promotion. Most of these functions go beyond the scope of this chapter, and information on them can be found in a range of comprehensive up-to-date reviews (Smith and Read 2008; Varma et al. 2017). The plant protection by mycorrhizas can be based upon several mechanisms (Whipps 2004), and the direct plant pathogens inhibition by fungal-derived bioactive SM is the objective of this subchapter.

Basidiomycetes form several mycorrhizal types with the most important ectomycorrhiza, typical for the majority of tree and shrub species playing key roles in the boreal and temperate biomes (Smith and Read 2008). In vitro studies of ectomycorrhizal (EM) basidiomycete bioactivity and biocontrol potential were popular in 1970–1990s, when the most data on the topic were obtained (Whipps 2004). Unfortunately, recently such type of research became somewhat neglected. A range of EM basidiomycetes, such as species of *Suillus*, *Laccaria*, *Lactarius*, *Pisolithus*, *Rhizopogon*, *Scleroderma*, and *Thelephora*, in vitro exhibited production of active soluble SMs against plant deleterious fungi and pseudofungi. Polyacetylene diatretyne nitrile was the main active compound against *Phytophthora* and *Pythium*, and it was shown that pine roots colonized with its producers turned out to be less vulnerable for pathogen zoospore infection compared to EM with other mycobionts or non-mycorrhizal ones. The axenic culture of *Suillus variegatus* was shown to produce other antifungal SM, volatile isobutanol and isobutyric acid (Curl and Truelove 1986).

Pisolithus arhizus (formerly known as *P. tinctorius*), the most widely applied commercial EM agricultural inoculum, is remarkable for producing antibiotics pisolithins A (*p*-hydroxybenzoylformic acid) and B ((R)-(−)-*p*-hydroxymandelic acid). Along with a few related compounds, these SMs were active against the significant number of phytopathogenic fungi both at spore and mycelial phases (Tsantrizos et al. 1991). The fungicidal mechanism suggested is cell turgor disruption. Two synthetic *S* enantiomers of mandelic acid obtained were the most effective in the pathogenic fungal growth arrest (Kope et al. 1991).

The most well-studied EM species with antifungal potential so far are *Laccaria* species and *Paxillus involutus* due to their comparatively easy maintenance under laboratory conditions and common occurrence (Whipps 2004). However, the research of their protective potential and its mechanisms are far from complete. *Paxillus involutus* was shown to induce 47% increase in colonized *Pinus resinosa* seedling resistance to the pine damping-off causative agent *Fusarium oxysporum* via some antifungal compound releasing (Duchesne et al. 1988). Oxalic acid turned out to be one of the compounds contributing to the antifungal effect (Duchesne et al. 1989), but other potential antifungals of *P. involutus* are still obscure. *Laccaria laccata* culture filtrate strongly inhibited spore germination in *Fusarium oxysporum* (Chakravarty and Hwang 1991), but the SM involved was not elucidated yet too.

However, the most possible hypotheses suggested in later studies, the plant production of antifungals induced by mycorrhization (Machón et al. 2009) is not suitable for the case of in vitro fungal activity detected.

A promising bioactive lactarane sesquiterpene rufuslactone was derived from *Lactarius rufus* fruit bodies (Luo et al. 2005b). As antifungal it outmatched the commercial fungicide carbendazim against plant pathogenic *Alternaria* strains, thus suggesting a prospect for analogue synthesis and future application.

It is obvious that EM fungi-derived bioactive compounds should not be disregarded in sustainable agriculture. To facilitate its proper usage in biocontrol ad hoc and as lead compounds, the greatest challenges to be addressed are recognizing the corresponding SM identity and its focused screening and not so easy delimitation of fungal chemical direct antagonistic effect against pathogens from EM-induced plant intrinsic resistance and the general plant performance improvement under natural conditions.

1.3.3 Nematicidal Metabolites of Basidiomycetes and Its Potential in Sustainable Agriculture

More than 4000 nematode species are plant pathogenic (predominantly soil-borne root pathogenic). These pests are of extreme economic importance being a cause of at least 12% worldwide food production annual losses (Askary and Martinelli 2015). Provided that a number of registered chemical nematicides affect a range of nontarget organisms and jeopardize soil ecosystems' normal functioning, the environment-friendly biocontrol method should be a promising alternative for the toxic chemical's usage. Fungal-nematode natural antagonism is based on the fungal ability to attack nematodes to prevent mycelium grazing or either to consume nematodes compensating nitrogen limitation. Nematode-preying (and consuming their prey with extracellular enzymes) and nematode-parasitic fungi are known as nematophagous, while nematode toxic (nematicidal) ones exhibit toxicity against nematodes without obligate further utilization of their victims. It is naturally enough to expect nematode toxicity in nematophagous fungi, but the recent studies have shown the presence of nematicidal SM in far wider spectrum of fungi, thus considering the activity against nematodes as a fungal defense strategy (Li and Zhang 2014; Askary and Martinelli 2015; Degenkolb and Vilcinskas 2016a).

Nematode-toxic fungi are numerous, comprising about 280 species of *Ascomycota* and *Basidiomycota* (Li and Zhang 2014), but some nematicidal ascomycetes are phytopathogenic or phytotoxic themselves (Degenkolb and Vilcinskas 2016a). Nematicidal SM are represented in 77 basidiomycete genera with about 160 species lacking plant deleterious effects in reasonable concentrations (Li and Zhang 2014). The most well-known and promising for biocontrol nematicidal basidial fungi SMs are summarized in Table 1.2.

White-rot-causing genus *Pleurotus* is the most well-studied nematophagous basidiomycete group by now, comprising 23 species with nematicidal activity (Li and Zhang 2014). It includes common edible cultivated species such as *P. ostreatus* and, along with this, is notable for excreting toxins to prey nematodes, such as the first detected SM (E)-2-decenedioic acid. Further compounds followed, and *S*-coriolic and linoleic acids derived from *P. pulmonarius* are considered to be the most potent and promising for application against phytopathogenic nematodes (Degenkolb and Vilcinskas 2016b). Herb-associated *P. eryngii* both with wood-inhabiting non-nematophagous *Cheimonophyllum candidissimum* are producers of nematicidal sesquiterpenoids cheimonophyllons (Table 1.2). It is notable that this *Pleurotus* species possesses an effective antifungal peptide eryngin too, thus representing a promising biocontrol agent for integrated management.

Some terrestrial basidiomycetes are known to be nematophagous too. Besides an ability to damage nematodes mechanically, *Coprinus comatus* was shown to produce seven nematicidal compounds under culture conditions. Two of them, 5-methylfuran-3-carboxylic acid and 5-hydroxy-3,5-dimethylfuran-2 (5H)-one, are highly effective against *Meloidogyne incognita*, the root-knot nematode pathogenic for a range of crops worldwide (Degenkolb and Vilcinskas 2016b).

Non-nematophagous, predominantly wood-inhabiting, basidiomycetes can exhibit notable nematicidal activity too. *Cheimonophyllum candidissimum* produces nontoxic cheimonophyllons for plants which became lead compounds for synthesis. Sesquiterpene dichomitin B from polyporoid *Dichomitus squalens* can be considered as an excellent lead SM with pronounced activity against plant pathogenic nematodes (Degenkolb and Vilcinskas 2016b). Effective and stable nematicidal cyclic dodecapeptides omphalotins from *Omphalotus olearius* mycelium and overmatching the commercial actinomycete-derived preparation ivermectin are discussed earlier. Terpenoid illinitone A derived from terrestrial *Limacella illinita* is considered as a promising agricultural nematicide too, but its activity was shown against the model free-living nematode species *Caenorhabditis elegans*, known for its sensitivity toward diverse SM (Degenkolb and Vilcinskas 2016b).

At present there are no widely applied commercial fungi-derived nematicides comparable to actinomycete-derived ivermectin (Li and Zhang 2014), but a number of basidiomycetes, listed above, have a strong potential for novel nematicide development. The nematode toxicity may be more widespread among basidial fungi than it was previously thought; and the culture collection screening with focus on the species proved bioactive in different ways, such as a popular medicine fungus *Wolfiporia cocos*, is a future challenge for urgent discovery of new active species and probably novel undescribed compounds too.

1.4 Screening for Novel Plant-Protective Basidiomycete Bioactive Metabolites

The strobilurins' triumph encourages the screening for novel promising compounds for plant protection. The enormous diversity of basidial fungi themselves and their SM as well provide an inexhaustible "Klondike" for researchers. The regions with mycobiota totally unexplored or surveyed "with half an eye" can be the most perspective in this field. There the biodiversity inventory could be coupled with assessment of fungal biochemistry potential. The situation has some in common with that at the dawn of novel actinomycete antibiotic search. This bacterial group was nearly unknown in 1950–1960s, and the disclosure of a novel compound suggested a description of a new species as well. Thereby the screening facilitated actinomycete taxonomy studies and biodiversity assessment.

Basidiomycete screening for bioactive SM became regular many years ago. Often the investigations of fruit bodies' chemical composition and products of basidial fungal cultures displaced the bioactivity research. Probably this led to the loss of many interesting and economically valuable natural compounds. SM screening can be accomplished by two different approaches. The first one implies the detection of the bioactive substance with standard test-organism set: bacteria, yeasts, and filamentous fungi. The second is focused upon SM targeting certain groups: plant pathogenic fungi, parasitic nematodes, insect pests, etc. The fungal material for screening procedure can vary too from field samples to axenic cultures, the latter causing a little disadvantage for symbiotrophs and some other fungal groups. Screening protocols usually consider the ecology of potential producers or concentrate at groups with poorly known biosynthetic potential. The latter supports the urge for marine, coprophilous, and stress-tolerant fungi. The publications dealing with the screening for basidiomycetes SM producers are rather numerous, so we can apply only to some typical ones.

Antifungal basidiomycete species active against plant pathogens were revealed in the Yunnan province, China, within the frame of bioactive SM research. The compounds diverse in their chemical structure were detected. One species has produced the bioactive SM grifolin, which was examined in details for its effects on pathogens' spores germination and mycelial growth. The experiments on plant defense were conducted (Liu 2002; Luo et al. 2005a).

Chilean basidiomycete culture collection (148 strains) was screened for antibacterial and antifungal SM producers. Activity was detected in 60% of species studied, and *Agaricales* and *Polyporales* orders proved to be the most promising groups (Aqueveque et al. 2010).

Wood-inhabiting fungi (51 cultures) from eucalypt plantations in Uruguay were examined for antifungal and antibacterial activity against plant pathogens. As a result eight cultures proved to be active (Barneche et al. 2016).

The interesting approach to plant pathogen inhibitor exploration was suggested by Thines et al. (2004). Many plant pathogenic fungi pass several stages during their life cycle, and if these differ significantly from vegetative mycelium, then they are potentially subject to fungitoxic plant protection treatment. In the case of *Magnaporthe grisea*, the stages preliminary to plant infection were examined, and the selective bioactive SMs inhibiting the signal transduction associated with appressoria formation were listed, while SMs inhibiting the pathogen growth within plant tissues or its sporulation were not recognized. The authors consider this approach as a perspective future trend.

1.5 Conclusion and Future Research Prospects

Basidiomycete bioactive SMs are undoubted headliners of modern medicine exhibiting enormous numbers of antiviral, antibacterial, antifungal, antitumor, and immunomodulating effects (Gargano et al. 2017). But in the field of plant growth promotion, they undeservedly obtained rather little attention from researchers and are generally underestimated. Basidiomycete-derived antifungals have a great potential for agriculture, and strobilurins have already proved their advantages at global scale. The nematicidal SM should be considered too, not rare being derived from the species considered active against fungi. One of the limitations for basidial fungi exploration and application, their recalcitrance to culture methods, now could be evaded via analogue synthesis lead by natural SM. In the field of plant protection, ectomycorrhizal guild SMs deserve more attention, for they are presumably required for competing with other fungi for root tips. Besides, regretfully artificial experimental conditions can mask perspective results and lead to misinterpretation of data obtained. So, the future research prospects and challenges can be outlined as:

- Regular biodiversity surveys, especially for regions previously ignored, for new fungal species
- Extensive screening for novel bioactive SM using the culture collections available with attention to small previously neglected taxa and, contrary, to species already exhibiting any activity
- Detailed analysis of all kinds of activities, for basidiomycetes tend to possess multiple effects (e.g., the route from medicine toward the agriculture or from fungicides to nematicides), and broadening the range of test objects
- Recognizing the SM-based bioactive effects per se and delimitation those from other forms of antagonism, especially in EM research
- Considering the species- and even strain-level variability of the bioactive effects and advances in the taxonomy to interpret phylogenetic relationship correctly
- Considering the ecology specificity and plasticity of potential producers and seek for close to natural experimental conditions

Acknowledgments Financial support by the Russian Science Foundation (RSCF) to Elena Voronina (program 14-50-00029) is gratefully acknowledged.

References

Anke T (1989) Basidiomycetes: a source for new bioactive secondary metabolites. In: Bushell ME, Gräfe H (eds) Bioactive metabolites from microorganisms. Progress in industrial microbiology, vol 27. Elsevier, Amsterdam, pp 51–66

Anke T (1995) The antifungal strobilurins and their possible ecological role. Can J Bot 73:S940–S945

Anke T, Oberwinkler F, Steglich W, Schramm G (1977) The strobilurins – new antifungal antibiotics from the basidiomycete *Strobilurus tenacellus*. J Antibiot 30:806–810

Anke T, Hecht HJ, Schramm G, Steglich W (1979) Antibiotics from basidiomycetes. IX. Oudemansin, an antifungal antibiotic from *Oudemansiella mucida* (Schrader ex Fr.) Hoehnel (Agaricales). J Antibiot 32:1112–1117

Anke T, Kupka J, Schramm G, Steglich W (1980) Antibiotics from basidiomycetes. X. Scorodonin, a new antibacterial and antifungal metabolite from *Marasmius scorodonius* (Fr.) Fr. J Antibiot 33:463–467

Anke T, Giannetti B-M, Steglich W (1982) Antibiotika aus Basidiomyceten, XV [1]. l-Hydroxy-2-nonin-4-on, ein antifungischer und cytotoxischer Metabolit aus *Ischnoderma benzoinum* (Wahl.) Karst. Z Naturforsch C 37:1–4

Anke T, Werle A, Bross M, Steglic W (1990) Antibiotics from basidiomycetes. XXXIII. Oudemansin X, a new antifungal E-beta-methoxyacrylate from *Oudemansiella radicata* (Relhan ex Fr.) Sing. J Antibiot 43:1010–1011

Anke T, Werle A, Zapf S, Velten R, Steglich W (1995) Favolon, a new antifungal triterpenoid from a *Favolaschia* species. J Antibiot 48:725–726

Anke T, Rabe U, Schu P, Eizenhofer T, Schrage M, Steglich W (2002) Studies on the biosynthesis of striatal-type diterpenoids and the biological activity of herical. Z Naturforsch C 57:263–274

Anke T, Werle A, Kappe RB, Sterner O (2004) Laschiatrion, a new antifungal agent from a *Favolaschia* species (Basidiomycetes) active against human pathogens. J Antibiot 57:496–501

Aqueveque P, Anke T, Anke H, Sterner O, Becerra J, Silva M (2005) Favolon B, a new triterpenoid isolated from the chilean *Mycena* sp. strain 96180. J Antibiot 58:61–64. https://doi.org/10.1038/ja.2005.7

Aqueveque P, Anke T, Saéz K, Silva M, Becerra J (2010) Antimicrobial activity of submerged cultures of Chilean basidiomycetes. Planta Med 76:1787–1791. https://doi.org/10.1055/s-0030-1249853

Askary TH, Martinelli PRP (eds) (2015) Biocontrol agents of phytonematodes. CABI, Wallingford

Avanzo P, Sabotič J, Anžlovar S, Popovič T, Leonardi A, Pain RH, Kos J, Brzin J (2009) Trypsin-specific inhibitors from the basidiomycete *Clitocybe nebularis* with regulatory and defensive functions. Microbiology 155:3971–3981. https://doi.org/10.1099/mic.0.032805-0

Bailey AM, Alberti F, Kilaru S, Collins CM, de Mattos-Shipley K, Hartley AJ, Hayes P, Griffin A, Lazarus CM, Cox RJ, Willis CL, O'Dwyer K, Spence DW, Foster GD (2016) Identification and manipulation of the pleuromutilin gene cluster from *Clitopilus passecerianus* for increased rapid antibiotic production. Sci Rep 6:25202. https://doi.org/10.1038/srep25202

Balba H (2007) Review of strobilurin fungicide chemicals. J Environ Sci Health B 42:441–451. https://doi.org/10.1080/03601230701316465

Barneche S, Jorcin G, Cecchetto G, Cerdeiras MP, Vázquez A, Alborés S (2016) Screening for antimicrobial activity of wood rotting higher basidiomycetes mushrooms from Uruguay against phytopathogens. J Med Mushrooms 18(3):261–267. https://doi.org/10.1615/IntJMedMushrooms.v18.i3.90

Bérdy J (2005) Bioactive microbial metabolites. A personal view. J Antibiot 58:1–26. https://doi.org/10.1038/ja.2005.1

Bérdy J (2012) Thoughts and facts about antibiotics: where we are now and where we are heading. J Antibiot 65:385–395. https://doi.org/10.1038/ja.2012.27

Bohnert M, Nutzmann HW, Schroeckh V, Horn F, Dahse HM, Brakhage AA, Hoffmeister D (2014) Cytotoxic and antifungal activities of melleolide antibiotics follow dissimilar structure-activity relationships. Phytochemistry 105:101–108. https://doi.org/10.1016/j.phytochem.2014.05.009

Chakravarty P, Hwang SF (1991) Effect of an ectomycorrhizal fungus, *Laccaria laccata*, on fusarium damping-off in *Pinus banksiana* seedlings. Eur J For Path 21:97–106. https://doi.org/10.1111/j.1439-0329.1991.tb00949.x

Chen HP, Liu JK (2017) Secondary metabolites from higher fungi. In: Kinghorn A, Falk H, Gibbons S, Kobayashi J (eds) Progress in the chemistry of organic natural products, vol 106. Springer, Cham, pp 1–201. https://doi.org/10.1007/978-3-319-59542-9_1

Chepkirui C, Richter C, Matasyoh JC, Stadler M (2016) Monochlorinated calocerins A-D and 9-oxostrobilurin derivatives from the basidiomycete *Favolaschia calocera*. Phytochemistry 132:95–101. https://doi.org/10.1016/j.phytochem.2016.10.001

Chu K, Xia L, Ng T (2005) Pleurostrin, an antifungal peptide from the oyster mushroom. Peptides 26:2098–2103. https://doi.org/10.1016/j.peptides.2005.04.010

Clough JM (1993) The strobilurins, oudemansins, and myxothiazols, fungicidal derivatives of β-methoxyacrylic acid. Nat Prod Rep 10:565–574

Clough JM (2000) The strobilurin fungicides – from mushroom to molecule to market. In: Wrigley SK, Hayes MA, Thomas R, Chrystal EJT, Nicholson N (eds) Biodiversity: new leads for the pharmaceutical and agrochemical industries. The Royal Society of Chemistry, Cambridge, pp 277–282

Curl EA, Truelove B (1986) The rhizosphere. Advanced series in agricultural sciences, vol 15. Springer, Berlin/Heidelberg

Daum RS, Kar S, Kirkpatrick P (2007) Fresh from the pipeline: retapamulin. Nat Rev Drug Discov 6:865–866. https://doi.org/10.1038/nrd2442

De Silva DD, Rapior S, Sudarman E, Stadler M, Xu J, Alias SA, Hyde KD (2013) Bioactive metabolites from macrofungi: ethnopharmacology, biological activities and chemistry. Fungal Divers 62:1–40. https://doi.org/10.1007/s13225-013-0265-2

Degenkolb T, Vilcinskas A (2016a) Metabolites from nematophagous fungi and nematicidal natural products from fungi as an alternative for biological control. Part I: metabolites from nematophagous ascomycetes. Appl Microbiol Biotechnol 100:3799–3812. https://doi.org/10.1007/s00253-015-7233-6

Degenkolb T, Vilcinskas A (2016b) Metabolites from nematophagous fungi and nematicidal natural products from fungi as an alternative for biological control. Part II: metabolites from nematophagous basidiomycetes and non-nematophagous fungi. Appl Microbiol Biotechnol 100:3813–3824. https://doi.org/10.1007/s00253-015-7234-5

Duchesne LC, Peterson RL, Ellis BE (1988) Interaction between the ectomycorrhizal fungus *Paxillus involutus* and *Pinus resinosa* induces resistance to *Fusarium oxysporum*. Can J Bot 66:558–562

Duchesne LC, Ellis BE, Peterson RL (1989) Disease suppression by the ectomycorrhizal fungus *Paxillus involutus*: contribution of oxalic acid. Can J Bot 67:2726–2730

Eilbert F, Engler-Lohr M, Anke H, Sterner O (2000) Bioactive sesquiterpenes from the basidiomycete *Resupinatus leightonii*. J Nat Prod 63:1286–1287

Engler M, Anke T, Sterner O (1998a) Production of antibiotics by *Collybia nivalis*, *Omphalotus olearius*, a *Favolaschia* and a *Pterula* species on natural substrates. Z Naturforsch C 53:318–324

Engler M, Anke T, Sterner O (1998b) Tintinnadiol, a sphaeroane diterpene from fruiting bodies of *Mycena tintinnabulum*. Phytochemistry 49:2591–2593

Erkel G, Anke T, Velten R, Gimenez A, Steglich W (1994) Hyphodontal, a new antifungal inhibitor of reverse transcriptases from *Hyphodontia* sp. (Corticiaceae, Basidiomycetes). Z Naturforsch C 49:561–570

Finking R, Marachiel MF (2004) Biosynthesis of nonribosomal peptides. Annu Rev Microbiol 58:453–488. https://doi.org/10.1146/annurev.micro.58.030603.123615

Florey HW, Chain E, Heatley NG, Jennings MA, Sanders AG, Abraham EP, Florey ME (1949) Antibiotics. A survey of penicillin, streptomycin, and other antimicrobial substances from fungi, actinomycetes, bacteria, and plants, vol I. Oxford University Press, Oxford

Gargano ML, van Griensven LJLD, Isikhuemhen OS, Lindequist U, Venturella G, Wasser SP, Zervakis GI (2017) Medicinal mushrooms: valuable biological resources of high exploitation potential. Plant Biosyst 151:548–565. https://doi.org/10.1080/11263504.2017.1301590

Gilardoni G, Clericuzio M, Tosi S, Zanoni G, Vidari G (2007) Antifungal acylcyclopentenediones from fruiting bodies of *Hygrophorus chrysodon*. J Nat Prod 70:137–139. https://doi.org/10.1021/np060512c

Hanson JR (2008) The chemistry of fungi. RSC Publishing, Cambridge

Hartley AJ, de Mattos-Shipley K, Collins CM, Kilaru S, Foster GD, Bailey AM (2009) Investigating pleuromutilin-producing *Clitopilus* species and related basidiomycetes. FEMS Microbiol Lett 297:24–30. https://doi.org/10.1111/j.1574-6968.2009.01656.x

Hautzel R, Anke H, Sheldrick WS (1990) Mycenon, a new metabolite from a *Mycena* species TA 87202 (basidiomycetes) as an inhibitor of isocitrate lyase. J Antibiot 43:1240–1244

Hibbett DS, Bauer R, Binder M, Giachini AJ, Hosaka K, Justo A, Larsson E, Larsson KH, Lawrey JD, Miettinen O, Nagy L, Nilsson RH, Weiss M, Thorn RG (2014) Agaricomycetes. In: McLaughlin DJ, Spatafora JW (eds) The mycota, Part A. Systematics and evolution, vol VII, 2nd edn. Springer, Berlin/Heidelberg, pp 373–429. https://doi.org/10.1007/978-3-642-55318-9_14

Hirota M, Shimizu Y, Kamo T, Makabe H, Shibata H (2003) New plant growth promoters, repraesentins a, B and C, from *Lactarius repraesentaneus*. Biosci Biotechnol Biochem 67:1597–1600. https://doi.org/10.1271/bbb.67.1597

Ishikawa NK, Fukushi Y, Yamaji K, Tahara S, Takahashi K (2001) Antimicrobial cuparene-type sesquiterpenes, enokipodins C and D, from a mycelial culture of *Flammulina velutipes*. J Nat Prod 64:932–934

Kavanagh F, Hervey A, Robbins WJ (1951) Antibiotic substances from basidiomycetes. VIII. *Pleurotus mutilus* (Fr.) Sacc. and *Pleurotus passeckerianus* Pilat. Proc Natl Acad Sci U S A 37:570–574

Keswani C (2015) Ecofriendly management of plant diseases by biosynthesized secondary metabolites of *Trichoderma* spp. J Brief Idea. https://doi.org/10.5281/zenodo.15571

Keswani C, Mishra S, Sarma BK, Singh SP, Singh HB (2014) Unravelling the efficient applications of secondary metabolites of various *Trichoderma* spp. Appl Microbiol Biotechnol 98:533–544

Kettering M, Valdivia C, Sterner O, Anke H, Thines E (2005) Heptemerones A-G, seven novel diterpenoids from *Coprinus heptemerus*: producing organism, fermentation, isolation and biological activities. J Antibiot 58:390–396. https://doi.org/10.1038/ja.2005.49

Knauseder F, Brandl E (1976) Pleuromutilins. Fermentation, structure and biosynthesis. J Antibiot 29:125–131

Kokubun T, Scott-Brown A, Kite GC, Simmonds MSJ (2016) Protoilludane, illudane, illudalane, and norilludane sesquiterpenoids from *Granulobasidium vellereum*. J Nat Prod 79:1698–1701. https://doi.org/10.1021/acs.jnatprod.6b00325

Kope HH, Tsantrizos YS, Fortin JA, Ogilvie KK (1991) P-Hydroxybenzoylformic acid and (R)-(−)-phydroxymandelic acid, two antifungal compounds isolated from the liquid culture of the ectomycorrhizal fungus *Pisolithus arhizus*. Can J Microbiol 37:258–264

Lauer U, Anke T, Sheldrick WS, Scherer A, Steglich W (1989) Antibiotics from basidiomycetes. XXXI. Aleurodiscal: an antifungal sesterterpenoid from *Aleurodiscus mirabilis* (Berk. & Curt.) Hohn. J Antibiot 42:875–882

Li G-H, Zhang K-Q (2014) Nematode-toxic fungi and their nematicidal metabolites. In: Zhang K-Q, Hyde KD (eds) Nematode-trapping fungi, Fungal diversity research series, vol 23. Springer, Dordrecht, pp 313–375. https://doi.org/10.1007/978-94-017-8730-7_7

Liermann JC, Kolshorn H, Antelo L, Hof C, Anke H, Opatz T (2009) Omphalotins E-I, five oxidatively modified nematicidal cyclopeptides from *Omphalotus olearius*. Eur J Org Chem 2009:1256–1262. https://doi.org/10.1002/ejoc.200801068

Liermann JC, Thines E, Opatz T, Anke H (2012) Drimane sesquiterpenoids from *Marasmius* sp. inhibiting the conidial germination of plant-pathogenic fungi. J Nat Prod 75:1983–1986. https://doi.org/10.1021/np300337w

Liu JK (2002) Biological active substances from mushrooms in Yunnan, China. Heterocycles 57:157–167. https://doi.org/10.3987/REV-01-543

Loiseleur O (2017) Natural products in the discovery of agrochemicals. Chimia 71:810–822. https://doi.org/10.2533/chimia.2017.810

Lorenzen K, Anke T (1998) Basidiomycetes as a source for new bioactive natural products. Curr Org Chem 2:329–364

Lũbken T, Schmidt J, Porzel A, Arnold N, Wessjohann L (2004) Hygrophorones A–G: fungicidal cyclopentenones from *Hygrophorus* species (Basidiomycetes). Phytochemistry 65:1061–1071. https://doi.org/10.1016/j.phytochem.2004.01.023

Luo DQ, Shao HJ, Zhu HJ, Liu JK (2005a) Activity in vitro and in vivo against plant pathogenic fungi of grifolin isolated from the basidiomycete *Albatrellus dispansus*. Z Naturforsch C 60:50–56

Luo DQ, Wang F, Bian XY, Liu JK (2005b) Rufuslactone, a new antifungal sesquiterpene from the fruiting bodies of the basidiomycete *Lactarius rufus*. J Antibiot 58:456–459. https://doi.org/10.1038/ja.2005.60

Ma B-J, Wu T-T, Ruan Y, Shen J-W, Zhou H, Yu H-Y, Zhao X (2010) Antibacterial and antifungal activity of scabronine G and H in vitro. Mycology 1:200–203. https://doi.org/10.1080/21501203.2010.508053

Machón P, Pajares JA, Diez JJ, Alves-Santos FM (2009) Influence of the ectomycorrhizal fungus *Laccaria laccata* on pre-emergence, post-emergence and late damping-off by *Fusarium oxysporum* and *F. verticillioides* on stone pine seedlings. Symbiosis 49:101–109. https://doi.org/10.1007/s13199-009-0015-0

Mayer A, Anke H, Sterner O (1997) Omphalotin, a new cyclic peptide with potent nematicidal activity from *Omphalotus olearius* I. Fermentation and biological activity. Nat Prod Lett 10(1):25–32

Mishra S, Singh A, Keswani C, Saxena A, Sarma BK, Singh HB (2015) Harnessing plant-microbe interactions for enhanced protection against phytopathogens. In: Arora NK (ed) Plant microbe symbiosis– applied facets. Springer, New Delhi, pp 111–125

Novak R, Shlaes M (2010) The pleuromutilin antibiotics: a new class for human use. Curr Opin Investig Drugs 11:182–191

Opatz T, Kolshorn H, Anke H (2008) Sterelactones: new isolactarane type sesquiterpenoids with antifungal activity from *Stereum* sp. IBWF 01060. J Antibiot 61:563–1567. https://doi.org/10.1038/ja.2008.75

Otto A, Porzel A, Schmidt J, Wessjohann L, Arnold N (2014) Penarines A-F, (*nor*-) sesquiterpene carboxylic acids from *Hygrophorus penarius* (Basidiomycetes). Phytochemistry 108:229–1233. https://doi.org/10.1016/j.phytochem.2014.09.005

Poulsen SM, Karlsson M, Johansson LB, Vester B (2001) The pleuromutilin drugs tiamulin and valnemulin bind to the RNA at the peptidyl transferase Centre on the ribosome. Mol Microbiol 41:1091–1099

Ranadive KR, Belsare MH, Deokule SS, Jagtap NV, Jadhav HK, Vaidya JG (2013) Glimpses of antimicrobial activity of fungi from world. J New Biol Rep 2(2):142–162

Sabotič J, Popovič T, Puizdar V, Brzin J (2009) Macrocypins, a family of cysteine protease inhibitors from the basidiomycete *Macrolepiota procera*. FEBS J 276:4334–4345. https://doi.org/10.1111/j.1742-4658.2009.07138.x

Sabotič J, Ohm RA, Künzler M (2016) Entomotoxic and nematotoxic lectins and protease inhibitors from fungal fruiting bodies. Appl Microbiol Biotechnol 100:91–111. https://doi.org/10.1007/s00253-015-7075-2

Schmidt-Dannert C (2014) Biosynthesis of terpenoid natural products in fungi. In: Schrader J, Bohlmann J (eds) Biotechnology of isoprenoids, Advances in biochemical engineering/biotechnology, vol 148. Springer, Cham, pp 19–61. https://doi.org/10.1007/10_2014_283

Schüffler A, Anke T (2009) Secondary metabolites of basidiomycetes. In: Anke T, Weber D (eds) Physiology and genetics XV: selected basic and applied aspects. Springer, Berlin, pp 209–231

Schüffler A, Anke T (2014) Fungal natural products in research and development. Nat Prod Rep 31:1425–1448. https://doi.org/10.1039/c4np00060a

Schüffler A, Wollinsky B, Anke T, Liermann JC, Opatz T (2012) Isolactarane and sterpurane sesquiterpenoids from the basidiomycete *Phlebia uda*. J Nat Prod 75:1405–1408. https://doi.org/10.1021/np3000552

Singh HB, Sarma BK, Keswani C (eds) (2016) Agriculturally important microorganisms: commercialization and regulatory requirements in Asia. Springer, Singapore

Singh HB, Sarma BK, Keswani C (eds) (2017) Advances in PGPR research. CABI, Wallingford

Smith SE, Read DJ (2008) Mycorrhizal symbiosis, 3rd edn. Academic, London

Spiteller P (2008) Chemical defence strategies of higher fungi. Chem Eur J 14:9100–9110. https://doi.org/10.1002/chem.200800292

Stadler M, Anke H, Sterner O (1994a) Six new antimicrobial and nematicidal bisabolanes from the basidiomycete *Cheimonophyllum candidissimum*. Tetrahedron 50:12649–12654

Stadler M, Mayer A, Anke H, Sterner O (1994b) Fatty acids and other compounds with nematicidal activity from cultures of basidiomycetes. Planta Med 60:128–132

Tang YZ, Liu YH, Chen JX (2012) Pleuromutilin and its derivatives-the lead compounds for novel antibiotics. Mini-Rev Med Chem 12:53–61

Thines E, Anke H, Weber RWS (2004) Fungal secondary metabolites as inhibitors of infection-related morphogenesis in phytopathogenic fungi. Mycol Res 108:14–25

Thongbai B, Surup F, Mohr K, Kuhnert E, Hyde KD, Stadler M (2013) Gymnopalynes A and B, chloropropynyl-isocoumarin antibiotics from cultures of the basidiomycete *Gymnopus* sp. J Nat Prod 76:2141–2144. https://doi.org/10.1021/np400609f

Tsantrizos YS, Kope HH, Fortin JA, Ogilvie KK (1991) Antifungal antibiotics from *Pisolithus tinctorius*. Phytochemistry 30:1113–1118

Turner WB, Aldridge DC (1983) Fungal metabolites II. Academic, New York

Varma A, Prasad R, Tuteja N (eds) (2017) Mycorrhiza – function, diversity, state of the art, 4th edn. Springer, Cham. https://doi.org/10.1007/978-3-319-53064-2

Von Jagow G, Gribble GW, Trumpower BL (1986) Mucidin and strobilurin a are identical and inhibit electron transfer in the cytochrome bc1 complex of the mitochondrial respiratory chain at the same site as myxothiazol. Biochemistry 25:775–780

Wang H, Ng T (2004a) Eryngin, a novel antifungal peptide from fruiting bodies of the edible mushroom *Pleurotus eryngii*. Peptides 25:1–5. https://doi.org/10.1016/j.peptides.2003.11.014

Wang H, Ng TB (2004b) Alveolarin, a novel antifungal polypeptide from the wild mushroom, *Polyporus alveolaris*. Peptides 25:693–696. https://doi.org/10.1016/j.peptides.2004.01.026

Wang H, Ng T (2006) Ganodermin, an antifungal protein from fruiting bodies of the medicinal mushroom *Ganoderma lucidum*. Peptides 27:27–30. https://doi.org/10.1016/j.peptides.2005.06.009

Wangun HVK, Dorfelt H, Hertweck C (2006) Nebularic acids and nebularilactones, novel drimane sesquiterpenoids from the fungus *Lepista nebularis*. Eur J Org Chem (7):1643–1646. https://doi.org/10.1002/ejoc.200500869

Whipps JM (2004) Prospects and limitations for mycorrhizas in biocontrol of root pathogens. Can J Bot 82:1198–1227. https://doi.org/10.1139/B04-082

Yamane M, Minami A, Liu C, Ozaki T, Takeuchi I, Tsukagoshi T, Tokiwano T, Gomi K, Oikawa H (2017) Biosynthetic machinery of diterpene pleuromutilin isolated from basidiomycete fungi. Chembiochem 18:2317–2322. https://doi.org/10.1002/cbic.201700434

Yang LP, Kean SJ (2008) Retapamulin: a review of its use in the management of impetigo and other uncomplicated superficial skin infection. Drugs 68:855–873

Zakharychev VV, Kovalenko LV (1998) Natural compounds of the strobilurin series and their synthetic analogues as cell respiration inhibitors. Russ Chem Rev 67:535–544

Zhu F, Qin C, Tao L, Liu X, Shi Z, Ma X, Jia J, Tan Y, Cui C, Lin J, Tan C, Jiang Y, Chen Y (2011) Clustered patterns of species origins of nature-derived drugs and clues for future bioprospecting. Proc Natl Acad Sci U S A 108:12943–12948. https://doi.org/10.1073/pnas.1107336108

Zjawiony JK (2004) Biologically active compounds from Aphyllophorales (polypore) fungi. J Nat Prod 67:300–310. https://doi.org/10.1021/np030372w