Chapter 9
Fungal Community for Novel Secondary Metabolites

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9.1 Introduction

Fungal communities have a vitally important role in our routine life, whether positive or negative (De Vries and Shade 2013). They are origins of lifesaving and life-enhancing drugs, food additives, and aromas, but they also have the potential to contaminate our crops and food or to cause serious infections (Gerke and Braus 2014). Microbes such as fungi, bacteria, plants, and some insects produce secondary metabolites (Kusari et al. 2013). These natural products are low molecular weight molecules that, differing from primary metabolites, are not indispensable for the survival of the organism but confer an advantage in specific habitats or during changes in environmental conditions (Lange 2015). Various secondary metabolites possess biological activities that range from beneficial to harmful (Brandt and Mølgaard 2001).

Advantageous secondary metabolites (SMs) include antifungal agents such as caspofungin (Macheleidt et al. 2016), antibacterial agents such as penicillin, anticancer drugs such as taxol, immunosuppressive drugs such as cyclosporine, or cholesterol-lowering drugs such as lovastatin (Li and Vederas 2009). A growing problem is the amazing current and future increases in resistance against established antibiotics as was foretold by the WHO (Brown and Wright 2016). Antibiotic use in clinical medicine, stock breeding, and agriculture leads to the development of multiresistances, especially in daily applications where various known antibiotics are ineffective (Chang et al. 2015). Thus, the innovation of novel drugs is essential (Li and Pan 2014). Various species of fungi such as *Aspergillus niger* are used for the large-scale fermentation of citric acid and gluconic acid and are industrially exploited as enzymes, food additives, and medicinal drugs (Dhillon et al. 2011).

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The fungus *Aspergillus oryzae* is used in Asian cuisine for the fermentation of soybeans, saccharification of rice, and production of alcoholic drinks and rice vinegars (Murooka and Yamshita 2008), and the fungus *Monascus purpureus* is used for a natural food coloring (Mapari et al. 2010). In food preparation that uses fungi, information about obtainable secondary metabolite gene clusters becomes even more significant as potentially harmful clusters of gene might lurk in the genome and represent a risk of alcoholism (Takeda et al. 2014). Some mycotoxins are produced by various *Aspergillus* sp., followed by citrinin and patulin, which are produced by *Aspergillus* and *Penicillium* sp., and *Fusarium*-specific toxins such as zearalenone, but the harmful secondary metabolites such as aflatoxins are prominent (Gerke and Braus 2014).

The mycotoxin-producing fungi in crop contamination lead to more than 10% loss in the yield of agricultural crops globally, representing a massive economic problem (Savary et al. 2012), although the pathogenic fungal spores that are harmful for both plants and animals can also cause various diseases. Allergic reactions are also induced by inhalation of fungal spores (Douwes et al. 2003). *Aspergillus fumigatus*, *Aspergillus flavus*, and *Aspergillus terreus* cause infection and can lead to invasive aspergillosis, which can be life threatening in immunocompromised patients (Stevens et al. 2000). Communities of fungi have the potential to produce various secondary bioactive metabolites used as therapeutic agents against several diseases directly or indirectly (Kusari et al. 2012). The production of secondary metabolites from the plant host with therapeutic potential such as taxol, podophyllotoxin, deoxypodophyllotoxin (Zhao et al. 2011), camptothecin and structural analogues, azadirachtin, hypericin, and emodin by fungal communities has been discovered (Chagas et al. 2018). Fungal communities produce bioactive compounds that are not only important from the ecological aspect but also from a biochemical and molecular position, especially those exclusive to their host plants (Berg and Smalla 2009).

The production of excess known and novel bioactive secondary metabolites may occur when exploiting the fungal community, such as modifying the available culture and process. The compounds produced by fungal communities might be optimized using controlled fermentation conditions, possibly leading to a cost-effective, environmentally friendly, continuous, and reproducible yield on commercial scale-up (Chan et al. 2003). The reduction of secondary metabolite production on repeated subculturing in axenic monoculture conditions needs to be described to establish, restore, and sustain the in vitro biosynthetic potential of endophytes, one of the key challenges. The fact that nearly all efforts to obtain secondary metabolites from fungal communities have so far been made by classical methodology, under axenic monoculture conditions, increased this problem (Kusari et al. 2012).The renewal of known secondary metabolites led occasionally to mostly overlooking the collection of cryptic products that are not formed naturally under standard in vitro conditions (Bills et al. 2013). To imagine the aforesaid challenges, in this perspective the basic principles of chemical networking approaches of fungal communities with their host plants highlight forthcoming directions and the virtually unlimited possibilities for discovery and the maintainable production of objective and not expected secondary metabolites exploiting fungal communities (Demain et al. 2017).

9.2 Collection and Detection Methods for Fungal Bioactive Compounds

The study of fungal metabolites has proceeded behind the study of other fungal metabolites because of scientific and organizational constraints (Morath et al. 2012). Moreover, the production of secondary metabolite (SM) production is bioactive (Stergiopoulos et al. 2013). The SM profiles fluctuate and depend entirely on the substrate, incubation period, nutrient media, temperature, and various environmental factors of given strains or species (López-González et al. 2015: Jurado et al. 2014). During the past half-century, there has been substantial progress on various compounds. The SMs of fungus determined by gas chromatography–mass spectrometry (GC-MS) and high performance liquid chromatography (HPLC) have been used recently because of their dominant separation and highly sensitive detection abilities (Turner et al. 2009). Tenax can be used for the concentration of headspace culture of solid adsorbent, followed by thermal desorption into the GC-MS (Bicchi et al. 2008). A library of mass spectra, database, or by comparative study of known standards of retention times and spectrum identified the SMs (Bino et al. 2004). In the headspace culture the volatile organic compounds adsorb or desorb by another method known as solid-phase micro-extraction (SPME) (David and Sandra 2007). This method decreases the time of preparation by combining extraction, introduction, and concentration into one step while increasing sensitivity over other extraction methods. Thus, this method has become popular recently (Hamelinck et al. 2005).

The living fungal cultures can be mechanized for headspace-SPME GC-MS by shortest profiling (Gao and Xu 2015). Novel volatile compounds cannot be determined by GC-MS, so this is one drawback. Simultaneous distillation extraction (SDE) of traditional methods such as vapor distillation and solvent extraction are used for the determination of secondary metabolites from *Penicillium roqueforti* and compared to the SPME method (Ridgway et al. 2010). Selected ion flow tube–mass spectrometry (SIFT-MS) in complex gas mixtures provides rapid broad-spectrum detection of trace secondary metabolites (Scotter et al. 2005). The production of secondary metabolites is detected from various species of fungi such as *Aspergillus*, *Candida*, *Mucor*, *Fusarium*, and *Cryptococcus* by the SIFT-MS technique (Morath et al. 2012). Proton transfer reaction–mass spectrometry (PTR-MS) and GC-MS instruments determine the profile of SMs released by *Xanthomonas* sp. The fungal SMs are quantified by using PTR-MS because it has fine detection ability and a fine-scale time response (Giannoukos et al. 2017). Moreover, examinations can be run without sample preparation, derivatization, or concentration in real time with the advantage of having sensitivities comparable to GC-MS (Hajslova et al. 2011).

This technique is also used for quantification of the SMs of *Muscodor albus* (Leelasuphakul et al. 2008). For further analysis and separation of the potential of secondary metabolites to identify innovative compounds produced by fungi, the sample is placed in a stainless steel column, then recovered and determined by nuclear magnetic resonance (NMR) spectroscopy (Strobel 2014). The "electronic nose" (E-nose) is an advanced technique used for bioactive compounds. An information processing unit with pattern recognition software and reference library is combined in the E-nose system by multisensory array (Carey et al. 2011). The SM production studies and results from examining numerous microbes and diversified communities of soil microbes of soil by several techniques are listed in Table 9.1.

9.3 Fungal Bioactive Compounds as Sources of Secondary Metabolites

For exploiting the bioactive metabolite compounds, fungi are the key resources (Harvey 2008). Between the fungi, biologically active metabolites are screened from the endophytes (Strobel and Daisy 2003). Without causing any disease symptoms, endophytic fungi inhabit within their host plants (Schulz et al. 2002). The low molecular weight compounds not required for growth in pure culture known as secondary metabolites are manufactured as a revision for specific functions in nature (Bérdy 2005). In the interactions of numerous metabolites between fungi and their plant hosts, such as signalling, defence, and instructions of the symbiosis, the SMs have a vital role in vivo (Tanaka et al. 2006).

Diverse classes of chemical substances such as steroids, xanthones, phenols, isocoumarines, perylene derivatives, quinones, furandiones, terpenoids, depsipeptides, and cytochalasines have been isolated from endophytic fungi (Nisa et al. 2015; Rana et al. 2018a; Suman et al. 2016; Yadav et al. 2018). Using non-ribosomal protein synthesis, such substances are synthesized through the polyketide pathway. A complex of *Burkholderia cepacia* non-ribosomal peptide-synthesized toxin is hemolytic and required for full virulence (Thomson and Dennis 2012). The various novel chemical structures produced by endophytes (51%) are significantly higher than the soil fungus (38%), as revealed from a literature survey suggesting that these habitually discounted endophytes are the novel source of bioactive secondary metabolites (Gnansounou et al. 2017). Special substances such as secondary metabolites are produced and in return demand nutrition. They are known to prevent the host from successfully attacking fungi and pests (Kaul et al. 2012; Nisa et al. 2015). With more resistance to nematodes, insects, and livestock, the fungal communities synthesize an array of metabolites for plants (Bassman 2004; Kaul et al. 2012).

Because of the production of phytohormones with specific endophytes inhabiting them, plants can grow faster and become so economical that they predominate in a specific environment (Herms and Mattson 1992; Rana et al. 2016, 2018a, b). The chemical compounds or secondary metabolites that are synthesized inside plants by the endophytes are associated with medicinal plants and can be exploited

Table 9.1 Methods applied for the detection of bioactive compounds from different fungal species

Methods	Organisms investigated	Habitat/ cultivation media	Bioactive compounds found	References
GC-MS	*Aspergillus* spp., *Cladosporium cladosporioides*, *Penicillium* spp.	Dichloran glycerol agar	Diverse bioactive compounds	El Sheikha et al. (2018)
GC-MS	Fungal community	Hyperthermic, hypersaline soils	Diverse bioactive compounds	Hock et al. (2018)
GC-MS	*Muscodor albus*	Modified minimal medium	Esters, alcohols, lipids, ketones	Enespa and Chandra (2017)
PTR-MS/ PTRTOF-MS	Fungal community	Temperate soil under different compost load	Diverse bioactive compounds	Enespa and Chandra (2017)
GC-MS	*Aspergillus fumigatus*	Modified minimal medium	Dimethyl sulfide (DMS), dimethyl disulfide (DMDS), 2,5-dimethylpyrazine (2,5-DMP), 1-undecene, 2-nonanone, 2-undecanone, and 2 aminoacetophenone (2-AAP)	Briard et al. (2016)
PTR-ToF MS, GC-MS, Electronic nose (e-nose) analysis	*Erwinia amylovora, Pseudomonas syringae* pv. *syringae*	Rooted plantlets, Murashige and Skoog (MS) medium	2-Ethoxy-2-methyl propane, 2,4,4-trimethyl-1-pentene and 2-methyl-furan	Cellini et al. (2016)
GC-MS	Fungal community	Hyperthermic, hypersaline soils	Diverse bioactive compounds	Miller et al. (2015)
GC-MS	*Muscodor albus* E-6 Endophytic fungus of *Guazuma ulmifolia*	Cultivated on potato dextrose agar (PDA)	Diverse bioactive compounds	Saxena et al. (2015)
GC-MSD (mass selective detector)	Fungal community	Orange waste	Monoterpenes, isoprene, other bioactive compounds	Li et al. (2012)
GC-MS	*Aspergillus* spp., *Cladosporium cladosporioides*, *Penicillium* spp.	Dichloran glycerol agar	Diverse bioactive compounds	Beck (2012)

(continued)

Table 9.1 (continued)

Methods	Organisms investigated	Habitat/ cultivation media	Bioactive compounds found	References
PTR-MS	*Shigella flexneri, Candida tropicalis*	Complex media	Diverse VOCs, several unidentified and some identified compounds of low molecular weight <150 μ	Effmert et al. (2012)
PTR-MS	Fungal community	Organic waste	Various bioactive compounds	Morath et al. (2012)
GC-MS	*Hypholoma fasciculare Resinicium bicolor*, wood-decaying fungi	Cultivated on malt broth	Diverse bioactive compounds	Sasidharan et al. (2011)
GC-MS/ growth inhibition of bacterial cultures	*Fusarium oxysporum* strain MSA 35	Agar (as described in experimental procedures)	Diverse bioactive compounds	Kai et al. (2010)
GC-MS	Fungal community	Different Mediterranean soils	Diverse bioactive compounds	Ens et al. (2009)
GC-MS	Fungal community	Different Mediterranean soils	Diverse bioactive compounds	Leff and Fierer (2008)
GC-MS	*Fusarium* spp.	MEA and PDA	Sesquiterpenes, mainly trichodiene	Perkowski et al. (2008)
GC-MS	*Muscodor albus* E-6 Endophytic fungus of *Guazuma ulmifolia*	Cultivated on PDA	Diverse bioactive compounds	Strobel et al. (2007)
GC-MS	*Fusarium* spp.	MEA and PDA	Sesquiterpenes, mainly trichodiene	Jeleń and Grabarkiewicz-Szczęsna (2005)
GC-MS	*Muscodor albus*	Endophytic fungus of *Cinnamonum*, cultivated on PDA	Diverse bioactive compounds	Ezra et al. (2004)
GC-MS	*Muscodor albus*	Endophytic fungus of *Cinnamonum*, cultivated on PDA	Diverse bioactive compounds	Stinson et al. (2003)
GC-MS	*Sclerotinia minor*, *S. sclerotium*, *S. rolfsii*	Lettuce and bean isolates, cultivated on PDA	Diverse bioactive compounds	Harvey and Sams (2000)

for curing many diseases (Compant et al. 2005; Strobel and Daisy 2003). The bioactive metabolites in a large number of endophytic fungi belong to diverse structural groups known as alkaloids, steroids, terpenoids, peptides, polyketones, flavonoids, quinols, phenols, xanthones, chinones, isocumarines, benzopyranones, tetralones, cytochalasines, perylene derivatives, furandiones, depsipeptides, and enniatines that have been extracted, characterized, and isolated (Tenguria et al. 2011). The novel structural groups represented by several of these are palmarumycins and a new benzopyroanone (Schulz et al. 2002). The fungi-produced secondary metabolites may vary with the biotope in which it grows and adopted, which varied with both habitat and substrate such as the manufacture of cyclosporine A, enchinocandin B, papulacandins, and verrucarins (de Carvalho et al. 2015). Screenings of natural products are the source of endophytic fungi, and in optimizing the search for secondary metabolites of new bioactive chemical compounds, it is relevant to consider that a fungus that synthesizes the SMs may resemble its particular ecological niche and metabolic interactions, which continue between the fungus and plant to enhance the production of secondary metabolites (Bérdy 2005; Cragg and Newman 2013).

In addition to being alternative sources for secondary metabolites known from plants, endophytes accumulate a wealth of other biologically active and structurally diverse natural products that are unprecedented in nature (Nisa et al. 2015; Proksch et al. 2010) It is now generally accepted that endophytes represent an important and largely untapped reservoir of unique chemical structures that have been modified through evolution and are believed to be involved in host plant protection and communication (Farrar et al. 2014). The fungal endophytes are known to release metabolites that mimic the structure and function of host compounds and produce plant growth hormones such as gibberellins (Hyde and Soytong 2008). A wide range of biological activities such as those of the antimicrobial agent hypericin and acetylcholinesterase inhibitor huperzine A are plant-associated secondary metabolites produced by prolific endophytes (Xiong et al. 2013), the antitumour agents taxol (Cai et al. 2015). Endophytes of bioprospecting offer promise to determine natural products with therapeutic value, which has increased attention from microbiologists, ecologists, agronomists, and chemists (Qin et al. 2011).

The endophytic fungi have great interest as potential producers of novel, biologically active products (Yadav 2018; Yadav et al. 2017; Strobel and Daisy 2003). The distribution of endophytic mycoflora differs with the host, known as an important component of biodiversity and also considered as endophytes (Khan et al. 2010). Globally, the necessity of new pharmaceutical products such as antibiotics, agrochemicals, and chemotherapeutic agents to manage the rising medicinal and ecological problems faced by mankind has increased interest in research on fungal community chemistry (Paladini et al. 2015). The mangrove plant *Rhizophora annamalayana* is the host of an endophytic fungus isolated and characterized for the production of taxol (Elavarasi et al. 2012). The extraction of secondary metabolite taxol is accomplished with ethyl acetate and characterized by chromatographic and spectrometric analysis (Fraser et al. 2000). The infrared (IR) spectrum values confirmed terpenoid functional groups and the violet-red represented by a thin-layer chromatographic plate (Milgram et al. 2007). In the leaf of *Cynodon dactylon*, an endophytic fungus, *Aspergillus fumigatus* CY018, was recognised for the first time (Liu et al. 2004).

The endophytic fungus *Taxomyces andreanae*, in producing paclitaxel from the yew plant *Taxus brevifolia*, set the stage for a more inclusive investigation of other species and other plants for the presence of paclitaxel-manufacturing endophytes (Pu et al. 2013), so as to apply this to developing the production of this pharmacologically important drug (Cohen 2002). The multi-billion dollar anticancer compound paclitaxel, produced by the yew plant (Chabner and Roberts 2005), has action against a broad range of tumour types (Kulbe et al. 2004), including breast, ovarian, lung, and head and neck cancers, as well as progressive forms of Kaposi's sarcoma (Vihinen and Kähäri 2002).

Production of loline alkaloids occurs by infection of grasses with endophytes which display restrictive and toxic effects towards herbivorous invertebrates and vertebrates and thus form a possible complex in protection of endophyte-infected grasses against herbivores (Saikkonen et al. 1998; Schardl et al. 2004). The three new antimicrobial metabolites and the indole-3-acetic acid (IAA) plant hormone were analysed from the culture of *Colletotrichum* sp., an endophyte isolated from inside the stem of *Artemisia annua* (Lu et al. 2000; Tan and Zou 2001). The isolation and characterization of various other chemical compounds such as ergosterol (I), 3b,5a,6b-trihydroxyergosta-7,2,2-diene (II), 3b-hydroxy-ergosta-5-ene (III), 3-oxo-ergosta-4,6,8 (14), 2,2-tetraene (IV), 3b-hydroxy-5a,8a-epidioxy-ergosta-6,2,2-diene (V), 3b-hydroxy-5a,8a-epidioxy-ergosta-6,9 (11), 2,2-triene (VI), and 3-oxoergosta-4-ene (VII) was also completed from the culture of a fungal community (Nisa et al. 2015). The growth inhibition of tested bacteria such as *Staphylococcus aureus, Bacillus subtilis, Pseudomonas* sp., and *Sarcina lutea* takes place by 1e3 and IIIeV chemical compounds (Son et al. 2016). Three species represent positive hits by screening of molecular markers and have the capability of producing taxol, which was authenticated by HPLC-MS. Among these three taxol-producing fungi, the yield of taxol was greater in *Guignardia mangiferae* HAA11 720 ng/l compared with *Fusarium proliferatum* HBA29 (240 ng/l) and *Colletotrichum gloeosporioides* TA67 (120 ng/ l), the fungal strain possessing antimicrobial activity (Liu et al. 2009; Chaturvedi 2015) (Table 9.2).

9.4 Antifungal Bioactive Compounds from a Fungal Community

Pathogenic fungi are controlled by secondary metabolites of some biocontrol fungi (Rohlfs and Churchill 2011). The mycoparasitism, nutrient competition, and secretion of other inhibitory compounds and hydrolytic enzymes by the various species of *Trichoderma* control the soil-borne fungal pathogens by various mechanisms (Benítez et al. 2004). The inhibition of growth and production of proteins from a wood-rotting basidiomycete *Serpula lacrymans* takes place from secondary metabolites secreted from *Trichoderma viride* and *T. aureoviride* (Schoeman et al. 1999). However, *T. pseudokoningii* showed no effect in any of the *Serpula lacrymans* isolate tests (Wheatley 2002; Bitas et al. 2013). The secondary metabolites secreted by

Table 9.2 Novel secondary metabolites from endophytic fungi

Fungal species	Origin	Secondary metabolites	Reported activities	References
Alternaria alternata	Terrestrial, grapevine leaves	9-Methoxy CPT	Antifungal, anticancer	Chakravarty and Gaur (2018)
Alternaria alternata RSF-6 L	Terrestrial, *Brassica napus*	Indole-3-acetic acid (IAA)	Antifungal, PGP	Yan et al. (2018)
Actinoallomurus fulvus	Terrestrial, *Capsicum frutescens*	Actinoallolides	Anti-trypanosomal	Nandi et al. (2019)
Penicillium manginii	Terrestrial, *Panax notoginseng*	Duclauxamide	Cytotoxicity	Bedi et al. (2018)
Cytospora sp.	Terrestrial, *Conocarpus erecta*	Cytoskyrins	BIA activity	Gao et al. (2018)
Periconia sp.	Terrestrial, *Annona muricata*	Pericoannosin	Anti-HIV	Gao et al. (2018)
Peyronellaea coffeae-arabicae	Terrestrial, *Pritchardia lowreyana*	Peyronellins	Cytotoxicity	Gao et al. (2018)
Mucor irregularis	Marine, *Rhizophora stylosa*	Rhizovarins	Cytotoxicity	Zhou and Xu (2018)
Rhizoctonia solani	Terrestrial, *Cyperus rotundus*	Solanioic acid	Antimicrobial	Dissanayake et al. (2016)
Fusarium sp. JZ-Z6	Terrestrial, *Fritillaria unibracteata*	Gallic acid	Antioxidant, anticancer	Pan et al. (2017)
Penicillium sp.	Terrestrial, *Catharanthus roseus*	Citreoviripyrone	Cytotoxicity	Jiménez-Romero et al. (2017)
Arthrinium sp. 0042	*Aquilaria subintegra*	oxo-Agarospirol	Antioxidant	Monggoot et al. (2017)
Penicillium brocae	Marine	Spirobrocazines	Antibacterial, cytotoxicity	Muharini et al. (2017)
Campylocarpon sp.	Marine, *Sonneratia caseolaris*	Campyridones	Cytotoxicity	Zhu et al. (2016)
Pestalotiopsis sp.	Marine, *Rhizophora mucronata*	Pestalotiopens	Antimicrobial	Xu (2015)
Paecilomyces variotii	Marine	Varioxepine	Antimicrobial	Zhang et al. (2015)
Trichoderma gamsii	Terrestrial, *Panax notoginseng*	Trichodermone	Cytotoxicity	Ding et al. (2014)
Paecilomyces variotii	Marine	Varioxepine	Antimicrobial	Meng et al. (2014)
Aspergillus sp.	Marine	Asperterpenols	Acetylcholinesterase inhibition	Xiao et al. (2013)

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Table 9.2 (continued)

Fungal species	Origin	Secondary metabolites	Reported activities	References
Aspergillus versicolor	Marine, green alga *Codium fragile*	Aspeverin	Marine plant growth inhibition	Ji et al. (2013)
Fusarium sp.	Terrestrial, *Melia azedarach*	Fusarimine	Antifungal	Gao et al. (2013)
Pestalotiopsis fici	Terrestrial	Chloropupukean olides	Cytotoxicity	Ebrahim et al. (2012)
Pestalotiopsis sp.	Terrestrial, *Clavaroids* sp.	Torreyanic acid analogue	Antifungal	Gutierrez et al. (2012)
Pestalotiopsis virgatula	Terrestrial, *Terminalia chebula*	Pestalospiranes	Antimicribial	Kesting et al. (2011)
Chalara alabamensis	Terrestrial, *Asterogyne martiana*	Asterogynins	Antimicribial	Rosa et al. (2013)
Pestalotiopsis sp.	Terrestrial, clavaroid species	Torreyanic acid analogue	Antibacterial	Zou et al. (2011)
Microsphaeropsis sp.	Terrestrial, *Lycium intricatum*	Microsphaerops ones	Antibacterial	Yang and Li (2011)
Pestalotiopsis fici	Terrestrial	Chloropestolide	Anti-HIV, cytotoxicity	Liu et al. (2010)
Nodulisporium sp.	Marine, alga	Noduliprevenone	Cytotoxicity	Greve et al. (2010)
Phaeosphaeria avenaria	Terrestrial	Phaeosphaeride	Inhibiting STAT3 activity	Weber (2009)
Phaeosphaeria avenaria	Terrestrial	Phaeosphaeride	Inhibiting STAT3 activity	Schlingmann et al. (2007)
Cytospora sp.	Terrestrial, *Conocarpus erecta*	Cytoskyrins	BIA activity	Gunatilaka (2006)
Cryptosporiopsis cf. *quercina*	Terrestrial, *Triptergyium wilfordii*	Cryptocin	Antifungal, Antibacterial	Strobel et al. (2005)
Fusarium pallidoroseum	Terrestrial	Apicidins	Antiprotozoal, anticancer	Somei and Yamada (2004)
Cryptosporiopsis cf. *quercina*	Terrestrial, *Triptergyium wilfordii*	Cryptocin	Antifungal	Strobel and Daisy (2003)
Pestalotiopsis sp.	Marine, *Rhizophora mucronata*	Pestalotiopens	Antimicrobial	Schulz et al. (1995)

various isolates of three *Trichoderma* spp. exhibited a degree of growth inhibition against a soil-borne fungal pathogen *Fusarium oxysporum* f. sp. *ciceris* that causes chickpea wilt disease (Gopalakrishnan et al. 2011). *F. oxysporum* strain MSA35 secreted secondary metabolites that enhanced the growth of lettuce plants and in the presence of ectosymbiotic bacteria also released the secondary metabolites that inhibit the growth of pathogenic strains of *F. oxysporum* (Enespa and Chandra 2017).

Antifungal metabolites revealed over time by the fermentation of dung-inhabiting fungi, or other compounds, are contrary to plant pathogenic fungi (Fu et al. 2012). The antagonistic features displayed by *Sordaria fimicola* against soil-borne pathogenic fungi such as *Pythium aphanidermatum* and *Dematophora necatrix* caused disease against the plant (Sarrocco 2016). The isolation of *S. fimicola* from wheat and ryegrass roots could reduce the size of these masses after inoculation with the take-all fungus (*Gaeumannomyces graminis* var. *tritici*) (Zhang et al. 2017). The submerged culture of *Coprinus heptemerus*, a basidiomycete, secreted seven diterpenoids, named heptemerones A to G that previously were not known to produce secondary metabolites (Molitor et al. 2012; Pettit et al. 2009). The chemical compounds were purified and tested for their antifungal activities, which inhibited the fungal germination, but this was highly dependent on the composition of the assay medium (Lavermicocca et al. 2000).

Four of the antifungal compounds exhibited plant protective activity in a leaf segment assay using *Magnaporthe grisea* as the pathogen (Kettering et al. 2005). *Podospora decipiens*, *Podospora curvicola*, and *Podospordaria tulasnei* have exposed antifungal activity by secondary metabolites against *Fusarium verticillioides*, *Aspergillus flavus*, and *F. verticillioides* and *Fusarium fujikuroi* (Cardwell et al. 2000), respectively. In agriculture, the demand is increasing for new antifungal compounds in the continuous search for new effective and natural fungicides for use against plant pathogens in integrated pest management (Dayan et al. 2009; Oerke 2006).

The academic institutions and agrochemical industries have been manufacturing new crop protection agents of microbial origin, which are safer for both the environment and consumers and more effective than the existing agents (Chandler et al. 2008). The naturally derived active pesticide ingredients are used in line with EC within the structure of achieving the sustainable use of pesticides by reducing the risk and impacts of their use on human health and the environment, and encouraging the use of integrated pest management and of unconventional techniques (Khater 2012). In this perspective, the fungal communities represent an uncultivated pool of bioactive metabolites, with chemical innovations that can be tested and further developed as active constituents in plant protection products (Lorenz and Eck 2005). Secondary metabolites-secreted antifungals by fungi against phytopathogenic fungi are given in Table 9.3 and Fig. 9.1.

9.5 Antibacterial Bioactive Compounds from Fungal Community

The fungal communities produced secondary metabolites that are larger than those of any other microorganism (Dean et al. 2005). These microorganisms occur in high frequency and are isolated from plants (Schippers et al. 1987). Numerous fungal genera seem to have a higher frequency of isolation and therefore a comparatively greater chance of an antibacterial substance being discovered in the species for

Table 9.3 Fungal bioactive compounds secreted by fungi against phytopathogenic fungi

Fungal antagonists	Bioactive compounds	Effects	Pathogenic fungi	References
Candida albicans	Farnesol	Inhibition of mycelial development, Apoptosis in altered morphology and reduced fitness	*Aspergillus nidulans*, *Fusarium graminearum*	Conrad et al. (2018)
Irpex lacteus, *Hypoxylon anthochroum* Blaci	Benzothiazole, cyclohexanol, *n*-decanal, dimethyl trisulfide, 2-ethyl-1-hexanol	Growth inhibition	*Alternaria solani*, *Botrytis cinerea*	Gao et al. (2017)
H. anthochroum Blaci	2-Methyl-5-(1-methylethyl)-bicyclohexan-2-ol, 2, 6-dimethyl-2, 4,6-octatriene	Inhibiting effect on growth of oomycetes	*Pythium ultimum*, *Phytophthora capsici*, *Alternaria solani*, *Fusarium oxysporum*	Ulloa-Benıtez et al. (2016)
Hypsizygus marmoreus	2-Methylpropanoic acid 2,2-dimethyl-1-(2-hydroxy-1- methylethyl) propyl ester	Inhibitory effect against conidial germination	*A. brassicicola (O-264)*	Oka et al. (2015)
Phomopsis sp.	Sabinene; isoamyl alcohol; 2-methyl propanol; 2-propanone	Worked as antibiotic effects	*Pythium*, *Phytophthora*, *Sclerotinia*, *Rhizoctonia*, *Fusarium*, *Botrytis*, *Verticillium*, *Colletotrichum*	Lee (2015)
Cladosporium cladosporioides CL-1	α-Pinene, β-caryophyllene, tetrahydro-2,2,5,5 tetramethylfuran, dehydroaromadendrene, sativene	Growth inhibition of mycelium	*Pseudomonas syringae*	Kamchiswamy et al. (2015)
Ampelomyces sp.	*m*-Cresol	Inhibition of mycelial growth	*Pseudomonas syringae* pv.	Naznin et al. (2014)

(continued)

Table 9.3 (continued)

Fungal antagonists	Bioactive compounds	Effects	Pathogenic fungi	References
Mycoleptodonoides aitchisonii	1-Phenyl-3-pentanone	Strongly inhibited the mycelial growth, spore germination	*Alternaria alternata*, *A. brassicicola*, *A. brassicae*, *Colletotrichum orbiculare*, *Corynespora cassiicola*	Nishino et al. (2013)
Epichloe typhina	Sesquiterpenes, chokols A–G	Fungitoxic	*Cladosporium phlei*	Kumar and Kaushik (2012)
Phoma sp.	Series of sesquiterpenoids, some alcohols, reduced naphthalene derivatives	Antifungal and fuel properties; some of the test organisms with the greatest sensitivity	*Verticillium*, *Ceratocystis*, *Cercospora*, *Sclerotinia*	Strobel et al. (2011)
Saccharomyces cerevisiae CR-1	3-Methylbutan-1-ol, 2-methylbutan-1-ol, 2-phenylethanol, ethyl acetate, ethyloctanoate	Inhibits vegetative development	*Guignardia citricarpa*	Fialho et al. (2010)
Saccharomyces cerevisiae	Ethyl acetate, 2-methylbutan-1-ol, 3-methylbutan-1-ol, 2-phenylethanol, ethyloctanoate	Growth inhibition	*G. citricarpa*	Verginer et al. (2010)
Trichoderma viride, *Trichoderma harzianum*	6-Pentyl-α-pyrone, β-1-3, glucanases	Phytotoxicity during seedling formation, seedling blight suppression	*Fusarium oxysporum*, *Rhizoctonia solani* (Israel), *Pythium ultimum* (USA)	El-Hasan and Buchenauer (2009)
Candida albicans	Farnesol	Inhibition of mycelial growth, apoptosis in altered morphology and reduced fitness	*Aspergillus nidulans*, *Fusarium graminearum*	Leveau and Preston (2008)

(continued)

Table 9.3 (continued)

Fungal antagonists	Bioactive compounds	Effects	Pathogenic fungi	References
Irpex lacteus	5-Pentyl-2-furaldehyde	Suppressed the growth	*F. oxysporum* f. sp. *lycopersici*, *Bulmeria graminis*, *Fusarium oxysporum*, *Colletotrichum Fragaria*, *Botrytis cinerea*	Koitabashi (2005)
Muscodor albus	Ethyl acetate, propanoic acid, 2-methyl-methyl ester, ethanol, acetic acid, 2-methylpropyl ester, propanoic acid, 2-methyl-butyl ester, 1-butanol, 2-methyl	Inhibited the growth of fungi	*Pythium ultimum*, *Phytophthora cinnamomi*, *Rhizoctonia solani*, *Ustilago hordei*, *Stagnospora nodorum*, *Sclerotinia sclerotiorum*, *Aspergillus fumigatus*, *Verticillium dahliae*, *Cercospora beticola*, *Xilaria* sp.	Ezra et al. (2004)

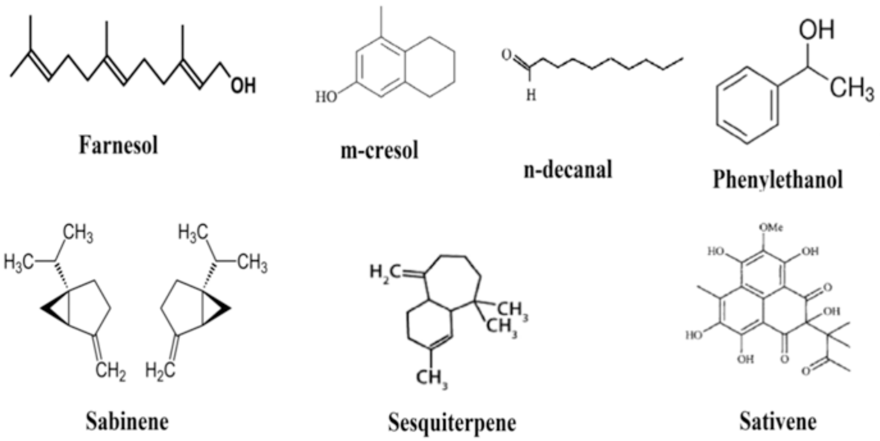
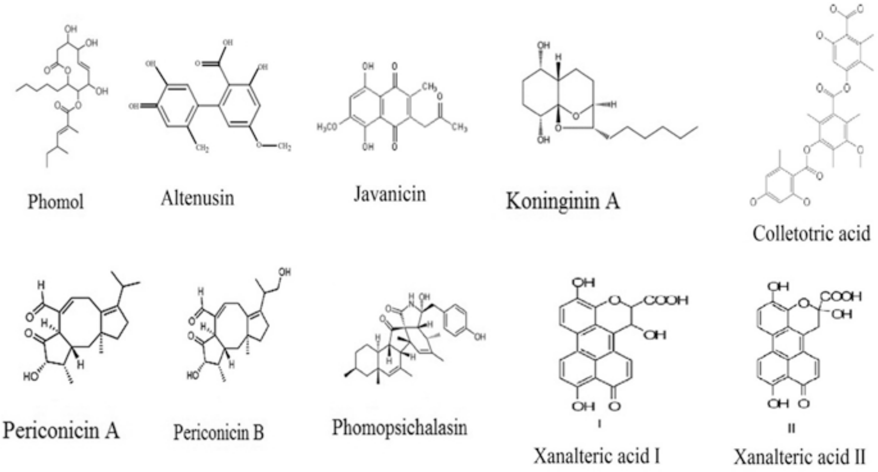


Fig. 9.1 Structural formulas of some of the antifungal bioactive compounds produced by fungal community

similar reasons (Radić and Štrukelj 2012). The various new secondary metabolites isolated and extracted from the endophytic fungus *Alternaria* sp. are 10-oxo-10*H*-phenaleno [1,2,3-de] chromene-2-carboxylic acids, xanalteric acids I and II (Fig. 9.2), and 11 other chemical compounds (Firáková et al. 2007). This fungus was isolated from the mangrove plant *Sonneratia alba* and exhibited weak antibacterial activity against *Staphylococcus aureus* (Debbab et al. 2010). The broad antimicrobial activity against several resistant pathogens with minimum inhibitory concentration (MIC) values in the range of 31.25–125 g/ml exhibited altenusin (Fig. 9.2) (Deshmukh et al. 2015).

Local people used *Aspergillus* sp. HAB10R12 for peptic ulcer and postpartum care was isolated from the root of *Garcinia scortechinii* (Ramasamy et al. 2010). The host plant *G. scortechinii* released xanthones that inhibit methicillin-resistant *Staphylococcus aureus* (MRSA) (Lin et al. 2017; Alurappa et al. 2018). *Aspergillus* sp. HAB10R12 showed antibacterial effect similar to that of the control antibiotics against *Micrococcus luteus* and *S. aureus* and significantly superior to gentamicin against *Bacillus subtilis* and *Escherichia coli* and cephalexin against *B. subtilis* (Ip et al. 2006). The naphthaquinone javanicin was highly functionalized (Fig. 9.2), with capable antibacterial activity, from an endophytic *Chloridium* sp. that was isolated from the surface-treated root tissues of *Azadirachta indica* (Kharwar et al. 2009).

Javanicin was active against *E. coli* and *Bacillus* sp. in the antibacterial test at a higher MIC value of 40 g/ml (Güllüce et al. 2003). This result could be an indicator of the selective antibacterial activity of javanicin, but it should be confirmed with additional testing (Rios and Recio 2005). The *Colletotrichum gloeosporioides* fungus, isolated from the medicinal plant *Vitex negundo* L., and three different extracts of hexane, ethyl acetate, and methanol were screened for their antibacterial activity



Phomol

Altenusin

Javanicin

Koninginin A

Colletotric acid

Periconicin A

Periconicin B

Phomopsichalasin

I

Xanalteric acid I

II

Xanalteric acid II

Fig. 9.2 Structural formulas of some of the antibacterial bioactive compounds produced by fungal community against methicillin-, penicillin-, and vancomycin-resistant clinical strains of *S. aureus* (Arivudainambi et al. 2011). The same endophytic fungus isolated from the stem of *Artemisia mongolica* showed on antimicrobial bioassay that colletotric acid (Fig. 9.2), isolated from the culture liquid, was inhibitory to the bacteria *B. subtilis*, *S. aureus*, and *Sarcina lutea* (Darabpour et al. 2012).

In the same way, the metabolites released from *Colletotrichum* sp., an endophytic fungus isolated from *Artemisia annua*, had strong antimicrobial action against the bacteria *B. subtilis*, *S. aureus*, *Sarcina lutea*, and *Pseudomonas* sp. (Alurappa et al. 2018). *Colletotrichum* sp. was also isolated from another source such as healthy tissues of *Lippia sidoides*, a medicinal plant used as an antiseptic (de Siqueira et al. 2011). The endophytic fungus *Colletotrichum gloeosporioides* isolated from *Alternaria alternata*, *Guignardia biwelli*, and *Phomopsis archeri* shows antimicrobial assay only on solid medium (Barbieri et al. 2014). The plant parts of *Garcinia mangostana* released metabolites similar to the activity of their particular hosts, and a screening of the antibacterial activity of endophytic fungi isolated from surface-pasteurized leaves and small branches of *Garcinia mangostana* was conducted (Carvalho et al. 2016). The short branches of *Taxus cuspidata* inhabited an endophytic fungus *Periconia* sp., and secreted fusicoccane diterpenes, named periconicins A and B (Fig. 9.2) (Zaiyou et al. 2017).

The ethyl acetate chemical was used for the purification of these compounds and was active in antibacterial assays (Septama and Panichayupakaranant 2015). Periconicin A compounds demonstrated significant antibacterial activity against *B. subtilis*, *S. aureus*, *Klebsiella pneumoniae*, and *Salmonella typhimurium* with MIC in the range of 3.12–12.5 g/ml, in contrast to gentamicin, with MIC in the range of 1.56–12.5 g/ml. Periconicin B displayed different antibacterial activity against the same strains of bacteria with MIC in the range of 25–50 g/ml (Heitefuss 2011). *Phomopsis* sp., an endophytic fungus that secretes a metabolite known as phomopsichalasin represents the first cytochalasin-type compound with a three-ring system replacing the cytochalasin macrolide ring (Fig. 9.2).

Disk diffusion assays against *B. subtilis* (12-mm zone of inhibition) and *S. aureus* (8-mm zone of inhibition) showed antimicrobial activity by the secreted metabolites (Clay 1988). Phomol, known as a novel antibiotic, was isolated from the fermentation broth of *Phomopsis* sp. strain E02018, which secreted a novel antibiotic known as phomol secreted by fermentation broth in the course of a screening of endophytic fungi from the medicinal plant *Erythrina* (Cowan 1999) (Fig. 9.2). However, it showed moderate antibacterial activity against *Arthrobacter citreus*, *Corynebacterium insidiosum*, and *Pseudomonas fluorescens* in the serial dilution assay and was not active against *E. coli* or *B. subtilis* (Munaganti et al. 2016). Helvolic acid is a significant component that exhibited the strongest antibacterial activity against *E. coli*, *B. subtilis*, *S. aureus*, and *S. haemolyticus*, with MIC values of 3.13, 3.13, 50, and 6.25 g/ml, respectively, which was isolated from the endophytic fungus *Pichia guilliermondii* and evaluated by microdilution colorimetric activity (Gómez-Rivera et al. 2018).

Panax notoginseng, a herbal plant inhabiting the PRE-5 strain and which is identified as *Trichoderma ovalisporum*, secreted koninginin A, (E)-2,3-dihydroxypropyl octadec-9-enoate, shikimic acid, cytosine ribonucleoside, and a compound considered to be adenine ribonucleoside from the culture broth (Fig. 9.2). Also, strain PRE-5 showed antibacterial activity against *S. aureus*, *B. cereus*, *M. luteus*, and *E. coli* (Dang et al. 2010).The culture extracts of the endophytic fungus *Xylaria* sp. YX-28, which is isolated from *Ginkgo biloba* L., was identified as 7-amino-4-methylcoumarin (Liu et al. 2008; Karaman et al. 2003). Determination of the antimicrobial activity of this chemical compound was observed by MICs and the agar-well diffusion method. The fungal community displayed strong antibacterial activity against pathogenic bacteria by all the secondary metabolites (Table 9.4).

9.6 Novel Approach to Obtaining Novel Bioactive Secondary Metabolites

Mutation, genetic manipulation, and cultural condition optimisation can improve the production of metabolites quantitatively and qualitatively (Hu et al. 2008). For the discovery of new metabolites and their biosynthetic pathways, the mutational approach is useful (Li and Vederas 2009).The generation of distinct phenotypes after analysis of mutants results from random mutagenesis, which is a powerful methodology to identify the essential factors for biological processes (Fiehn et al. 2000). For basic research and practical applications this self-assured genetic method is very important (Eisenstein 1990). A particularly increased sequence allowed by NGS techniques reduced the costs, thus qualifying the genomes of the mutant to be sequenced to identify affected genes (Meldrum et al. 2011).

Mutation identification strategies through whole-genome sequencing have been used for several model organisms, such as *Neurospora crassa* (Baird et al. 2008; Borkovich et al. 2004), with the premise that it is a efficient and rapid means to discover the mutations that are responsible for specific phenotypes (Letai et al. 1992). For survival, fungal communities must adapt to environmental stress, and a deeper understanding of the regulation and evolution of fungal stress response systems may lead to improved novel antifungal drugs and technologies (Frey-Klett et al. 2011).

Infrequently, the observation of a metabolic profile under standard fermentation does not reflect the number of anticipated biosynthesis genes of microorganisms, in that some loci remain silent (Knight et al. 2003). Because a reservoir of potentially bioactive compounds represents cryptic gene clusters, cryptic natural products strategies have been designed by triggering the biosynthetic pathways (Scherlach and Hertweck 2009). The transcription factors that mediated the fungal response to environmental cues such as nutrient availability, pH, light, and both biotic and abiotic stress are regulated by their secondary metabolites (Reverberi et al. 2010). To collect novel metabolites, the metabolic pathways of fungi are changed by the fermentation pathway (Papagianni 2004). By the addition of chromatin-modulating agents such as histone deacetylase or DNA methyl transferase inhibitors to fungal

Table 9.4 Fungal community producing metabolites with antibacterial activity

Endophytic fungal strain	Host plant(s) (family), plant part or tissue	Habitat of the host plant	Crude extract/isolated metabolite	Test bacteria	Type of test	Reference
49 endophytic fungi: The most active of the isolated strains: *Fusarium oxysporum* strain YNDC05 *Fusarium oxysporum* strain YNDC11 *Dictyosporium*	*Dracaena cochinchinensis* (Lour.) S.C. Chen (Asparagaceae); Ns *Dracaena cambodiana* Pierre ex Gagnep (Asparagaceae); ns	Yunnan Province, Hainan Province and Beijing, China	Ethanol extract of culture broth	*B. subtilis* (No. 1.0088), *S. aureus* (No.1.0089), *E. coli* (No. 1.2385)	Agar well diffusion method	Zheng et al. (2017)
Acremonium sp., *Diaporthe* sp., *Hypoxylon* sp., *Pestalotiopsis* sp., *Phomopsis* sp., *Xylaria* sp.	*Aegiceras corniculatum*, *Avicennia alba*, *Avicennia officinalis*, *Bruguiera gymnorrhiza*, *Bruguiera parviflora*	Mangrove areas in the south of Thailand in Satun, Songkhla, Surat Thani and Trang Provinces	Ethyl acetate crude extract of culture medium Ethyl acetate and hexane extract of fungal mycelium	*S. aureus* ATCC25923 A clinical isolate of MRSA SK1, *E. coli* ATCC25922, *P. aeruginosa* ATCC27853	Microdilution method according to a modification of Clinical and Laboratory Standards Institute (CLSI) M7-A4	Martinez-Klimova et al. (2017)
Xanthomonas oryzae	Oryzae	Rice field	Lauric acid, tridecanoic acid, myristic acid	*Bacillus* strain D13	diffusion method	Muniyan and Gurunathan (2016); Chandra and Singh (2016)

15 endophytic fungi with antibacterial activity	*Dracaena cambodiana* (Asparagaceae); leaf, root and stem *Aquilaria sinensis* (Lour.) Spreng. (Thymelaeaceae); leaf, root and stem	Jinghong city, Xishuangbanna prefecture, Yunnan, China	Crude extract	*B. subtilis* As 1.308, *E. coli* As 1.355, *S. aureus* As 1.72.	Agar diffusion test	Bezerra et al. (2015)
13 isolates of *Phomopsis* sp.	*Aspidosperma tomentosum* MART. (Apocynaceae); leaf Spondias mombin L. (Anacardiaceae); twig	Rio de Janeiro city (Morro do Entorno, Pedra do Marinheiro) and the Brazilian Amazon forest near Redenc, ao (Para state)	Ethyl acetate crude extracts of cultivation broth	*E. coli* (ATCC 25922), *P.aeruginosa* (ATCC 27853), *S. aureus* (ATCC 25,923)	Bioautographic TLC agar-overlay assay	Dokuparthi and Manikanta (2015)
Phomopsis sp. (internal strain no. 8966)	*Notobasis syriaca* (Asteraceae)	ns	Phomosine K, Phomosine A, phenylalanine amide, 2-hydroxymethyl-4,5,6 trihydroxycyclohex-2-en	*E. coli*, *B. megaterium*	Agar diffusion assays; Microdilution method in a 96-well microplate	Radić and Štrukelj (2012)
Phomopsis sp.	*Cistus salviifolius* (internal strain 7852) (Cistaceae)	ns	Pyrenocines J-M	*E. coli*, *B. megaterium*	Agar diffusion method	Radić and Štrukelj (2012)

(continued)

Table 9.4 (continued)

Endophytic fungal strain	Host plant(s) (family), plant part or tissue	Habitat of the host plant	Crude extract/isolated metabolite	Test bacteria	Type of test	Reference
Microsphaeropsis sp. strain 7177	*Zygophyllum fortanesii* (Zygophyllaceae); ns	Gomera, Spain	Fusidienol A 8-Hydroxy-6-methyl-9-oxo-9H-xanthene-1-carboxylic acid methyl ester	*E. coli*	Agar diffusion assay	Abreu et al. (2012)
24 endophytic fungi; *Microdiplodia hawaiiensis* CZ315 (most active isolated strain RGM-02)	*Garcinia mangostana* L. (Clusiaceae); leaf and small branch	Bogor Botanical Gardens, Indonesia	Crude ethyl acetate extracts	*S. aureus* (ATCC 25923), *B. subtilis* (ATCC 6633), *E. coli* (ATCC 25922), *P. aeruginosa* (ATCC 27,853), *S. typhi* (ATCC 14028), *M. luteus* (ATCC 10240)	Disc diffusion method; twofold microtiter broth dilution method	Radji et al. (2011)
Fusarium sp., *Phoma* sp., *Epicoccum nigrum*	*Dendrobium devonianum* Paxton (Orchidaceae); stem and root *Dendrobium thyrsiflorum* (Orchidaceae); stem and root	Longling, Vietnam	Crude ethanol extract of fermentation broth	*E. coli*, *B. subtilis*, *S. aureus*	Agar diffusion method	Xing et al. (2011)
14 species, mainly *Colletotrichum gloeosporioides*, *Alternaria alternata*, *Guignardia bidwelli*, *Phomopsis archeri* and *Drechslera dematioidea*	*Lippia sidoides* Cham. (Verbenaceae); Leaves and stems	Experimental Station of the Agropecuary Research Company of Pernambuco in Carpina-PE, Brazil	Fungal mycelium	*S. aureus* (ATCC-6538), *B. subtilis* (UFPEDA-16), *E. coli* (ATCC-25922).	Antimicrobial assay using a solid medium (Ichikawa 1971)	De Siqueira et al. (2011)

Colletotrichum gloeosporioides	*Vitex negundo* L. (Lamiaceae); leaf	Botanical Garden, Virudhunagar, Tamil Nadu, India	Hexane crude extract Ethyl acetate crude Methanol crude extract	*S. aureus* (MTCC 3160), *B. subtilis* (MTCC 619), *E. coli* (MTCC 4296), *P. aeruginosa* (MTCC 2488), 10 clinical strains of *S. aureus* obtained from Bose Clinical Laboratory and X-ray (India)	Kirby–Bauer disk diffusion test; Paper disk diffusion method; Broth microdilution method in a 96-well microplate	Arivudainambi et al. (2011)
Pichia guilliermondii Ppf9	*Paris polyphylla* var. *yunnanensis* (Franch) Hand.-Mazz. (Trilliaceae); rhizome	Kunming, China	Helvolic acid	*E. coli* (ATCC 29425), *B. subtilis* (ATCC 11,562), *S. aureus* (ATCC 6538), *S. haemolyticus* (ATCC 29970)	A modified microdilution-colorimetric assay, using the chromogenic MTT reagent	Zhao et al. (2010)
Alternaria sp. strain JCM9.2	*Sonneratia alba* J.E. Smith (Sonneratiaceae); leaf	Dong Zhai Gang Mangrove Garden on Hainan Island, China	Xanalteric acid I Xanalteric acid II Altenusin	*E. coli*, *E. faecium*, *Enterococcus cloacae*, *S. aureus*, *S. pneumonia*, *P. aeruginosa*, *K. pneumonia*	Dilution assay	Kjer et al. (2009)
Chloridium sp. (J.F.H. Beyma) W. Gams & Holubova-Jchova	*Azadirachta indica* A. Juss. (Meliaceae); root	Varanasi district, India	Javanicin	*E. coli*, *Bacillus* sp., *P. aeruginosa*, *P. fluorescens*	Microdilution method in a 96-well microplate	Kharwar et al. (2009)

(continued)

Table 9.4 (continued)

Endophytic fungal strain	Host plant(s) (family), plant part or tissue	Habitat of the host plant	Crude extract/isolated metabolite	Test bacteria	Type of test	Reference
Xylaria sp. YX-28	*Ginko biloba* L. (Ginkgoaceae); twig	Jiangsu and Shandong Provinces, China	7-Amino-4-methylcoumarin	*S. aureus*, *E. coli*, *S. typhi*, *S. typhimurium*, *S. enteritidis*, *Aeromonas hydrophila*, *Yersinia* sp., *V. anguillarum*, *Shigella* sp., *V. parahaemolyticus*	Twofold serial dilutions method	Liu et al. (2008)
Fusarium equiseti, *Guignardia vaccinii*	*Garcinia mangostana* L. (Clusiaceae); leaf, stem, root, fruit, and flower *Garcinia parvifolia* (Miq.) Miq. (Clusiaceae); leaf, stem, root, fruit, and flower	Sungai Rengit Village, Johor, Malaysia	Filtered broth suspension	*S. aureus*, *Listeria monocytogenes*, *B. subtilis*, *Aeromonas hydrophila*, *S. faecalis*	Well diffusion assay	Rukachaisirikul et al. (2008)
Guignardia sp. IFB-E028	*Hopea hainanensis* Merrill & Chun (Dipterocarpaceae)	Hainan Island, China	Monomethylsulochrin Rhizoctonic acid Guignasulfide	*H. pylori*	Agar diffusion method	Mégraud and Lehours (2007)

Aspergillus sp. strain CY725	*Cynodon dactylon* (L.) Pers. (Poaceae); leaf	Sheyang Port on the Yellow Sea	Helvolic acid Monomethylsulochrin Ergosterol 3_-Hydroxy-5_,8_-epidioxy-ergosta-6,22-diene	*H. pylori* (ATCC 43,504), Five clinical isolates obtained from antral biopsies of child and adult patients, *B. subtilis, P. fluorescens, E. coli*, *S. lutea*, *S. aureus*	Disk diffusion method	Li et al. (2005)
Rhizoctonia sp. strain Cy064	*Cynodon dactylon* (L.) Pers. (Poaceae); leaf	Jiangsu Province, China	Rhizoctonic acid Monomethylsulochrin Ergosterol 3-,5-,6-Trihydroxyergosta-7,22-diene	*H. pylori* (ATCC 43,504), Five randomly selected clinical strains from antral biopsies from children and adults	Agar dilution method	Ma et al. (2004)
Phoma sp. NG-25	*Saurauia scaberrinae* (Actinidiaceae); stem	Central highlands of Papua New Guinea	Phomodione Usnic acid Cercosporamide	*S. aureus* (ATCC 25,923), *E. coli* (Life Technology 18,290–015)	Disk diffusion assay	Yılmaz et al. (2004)
Colletotrichum sp.	*Artemisia annua* L. (Asteraceae); stem	ns	6-Isoprenylindole-3-carboxylic acid 3b,5a-Dihydroxy-6bacetoxy- ergosta-7,22-diene 3b,5a-Dihydroxy-6bphenylacetyloxyergosta-7,22-diene	*B. subtilis*, *S. aureus*, *Sarcina lutea*, *Pseudomonas* sp.	Paper-disk assay on LB	Lu et al. (2000)

ns not specified, *MTT* 3-(4,5-dimethylthiazol-2-yl)-2,5-dephenyl tetrazolium bromide cultures, epigenetic remodeling of fungal secondary metabolites can be achieved (Deepika et al. 2016). In *Cladosporium cladosporioides*, the production of new biomolecules enhanced chemical diversity, with the advantage that this technique does not require strain-dependent genetic manipulation and can be applied to any fungal strain (De la Rosa-García et al. 2018; Spina et al. 2018). Because of the complexity of microbial extracts, advanced analytical methods such as mass spectrometry and metabolomics are fundamental to detect and identify coculture-induced metabolites (Dettmer et al. 2007).

The nanospray desorption electrospray ionisation (n-DESI) combination and imaging mass spectrometry (IMS) have led to the monitoring of metabolite production from live microbial colonies within bacterial communities, thus identifying mass spectral molecular networking when different species coexist (Stasulli and Shank 2016). With a peptidogenomic approach the combination of IMS provides insight into the inter-kingdom interaction between *Pseudomonas aeruginosa* and *Aspergillus fumigatus* at a molecular level, thus allowing the visualisation and identification of metabolites secreted by these microorganisms as grown on agar (Moree et al. 2012).

9.7 Conclusion and Future Prospects

Fungal communities are very diverse and abundant in the environment, and thus they are a versatile reservoir of metabolites with new structures and new bioactivities that can be of potential use as leading compounds to manufacture new modern medicines. Sample collection and fungal cultivation methods in other environments such as terrestrial soil and freshwater and marine areas are very difficult: more fungi have been cultivated from these environments. A potential source for natural bioactive compound or secondary metabolites is provided by these fungal communities rather than a new drug to be extracted. Secondary metabolites extracted from the fungal communities of plant inhabitants with broad bioactivities, such as antifungal, antibacterial, anticancer, antiviral, anti-larval settlement, and cytotoxic activity, have been featured in the literature. In the natural ecosystem these bioactive compounds not only help any environmental fungus to defend against predators, but also have the potential of becoming treatments for human diseases and probes for new biological targets. This chapter indicates that study of the community of fungi characterized by their bioactive metabolites is underway, which is of increased importance as there is an urgent need for new drugs to overcome emerging and drug-resistant diseases.

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