

# Chapter 12

## Recent Progress on *Trichoderma* Secondary Metabolites



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### 12.1 Introduction

*Trichoderma* Pers. (Ascomycota, Sordariomycetes, Hypocreales, teleomorph *Hypocrea* Fr.) species are frequently found on dead wood and bark, on other fungi, and in soil and living as endophytes within healthy plant roots, stems, and leaves (Al-Askar et al. 2012, 2014; Mukherjee et al. 2013; Salem and Abdel-Azeem 2014).

*Trichoderma* plays a significant role in various ecosystems (Klein and Eveleigh 1998). Species of this genus are commonly found in soil, on decaying wood, and occasionally on other fungi. They are important for humans due to their applications in the production of enzymes, antibiotics, and heterologous proteins for food, feed, textile, and biofuel industries (Liu et al. 2016; Darmasiwi et al. 2016; He et al. 2018), biocontrol of plant pathogens (Saber et al. 2017; El-Sharkawy et al. 2018; Swain et al. 2018), and treatment of water or soil pollutions (Harman et al. 2004). Nevertheless, some species are causal agents of green mold disease in mushroom cultivation (Komoń-Zelazowska et al. 2007) or even as opportunistic human pathogens (Kredics et al. 2003; Sandoval-Denis et al. 2014). Many taxa are treated as agents for improving seed germination and nutrient use efficiency and breaking of seed dormancy, as well as source of transgenes and herbicides, and are long known to improve plant growth through the production of certain secondary metabolites (Zeilinger et al. 2016; Patle et al. 2018).

Taxonomy of *Trichoderma* traces back to 1794 when the genus was established. Its species concepts were problematic due to their similarities in culture characteristics. The first serious attempt to establish clear species concepts was made by Rifai

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(1969) who divided the genus into nine “species aggregates” based on morphology. In the following years, Bissett (1984, 1991a, b, c) conducted detailed studies and divided *Trichoderma* into five sections based also on morphological features, which was later proved to be insufficient to differentiate species (Kindermann et al. 1998; Kullnig-Gradinger et al. 2002). With development of molecular techniques, DNA sequences were applied in exploring the phylogenetic relationships among species of the genus (Kindermann et al. 1998). Species of the genus have been divided into 17 clades, as well as scattered independent lineages, according to phylogenetic information (Zhu and Zhuang 2014; Jaklitsch and Voglmayr 2015; Qin and Zhuang 2016a). Previous studies showed also that fungi in the same clades may share certain similar morphological features in addition to sequence data.

Among these clades, the *Trichoderma* clade is the largest and comprises more than 70 species. The Harzianum, Longibrachiatum, and Viride clades are among the largest and most diverse clades of the genus. The Harzianum clade includes several morphologically cryptic but biologically distinct species. Recently 15 species were recently added to the clade (Chen and Zhuang 2017a), although relationships among species of the clade need further research. Chen and Zhuang (2017b) introduced seven new species of the genus *Trichoderma* belonging to the Viride clade from soil samples of different regions in China. In 2018, Zhang and Zhuang introduced three new species during their field surveys in central and southwestern China, namely, *T. acremonioides*, *T. rugosum*, and *T. subalni*, which are located, respectively, in the Viride, Longibrachiatum, and Harzianum clades. Up to now, about 295 *Trichoderma* species have been described based on combined analyses of phylogenetic and morphological data (Bissett et al. 2015; Montoya et al. 2016; Qin and Zhuang 2016a, b, c; Qin and Zhuang 2017; Chen and Zhuang 2017a, b; Zhang and Zhuang 2017, 2018).

*Trichoderma* spp. display antimicrobial activity against an important number of bacteria, yeasts, and filamentous fungi (Vizcaíno et al. 2005), in which numerous and varied secondary metabolites (SMs), such as peptaibols, gliotoxin, gliovirin, polyketides, pyrones, and terpenes, may be involved (Vinale et al. 2006, 2009; Xiao-Yan et al. 2006). Considering the structures of *Trichoderma* antibiotic molecules present in nature, two main types have been distinguished: (1) low-molecular-weight and volatile metabolites, including simple aromatic compounds, some polyketides such as pyrones and butenolides, volatile terpenes, and isocyanate metabolites, all of them relatively nonpolar substances with a significant vapor pressure, and (2) high-molecular-weight polar metabolites, including peptaibols and diketopiperazine-like gliotoxin and gliovirin compounds, which may exert their activity through direct interactions by means of contact between *Trichoderma* spp. and their antagonists (Sivasithamparam and Ghisalberti 1998; Szekeres et al. 2005; Reino et al. 2007).

Over the years, numerous *Trichoderma* SMs have been isolated and their structures determined in analytical studies. More than 120 *Trichoderma* SMs structures have been reported (Sivasithamparam and Ghisalberti 1998; Reino et al. 2007). However, quantifying the exact number of SMs produced by *Trichoderma* spp. is not an easy task since they can produce more than 1000 compounds, depending on the strain, the environmental conditions, and the sensitivity of the detection method.

In recent years, information about the biosynthetic pathways of *Trichoderma* SMs and aspects regarding fungal metabolism and ecological interactions have begun to emerge from genetic and genomic studies. As reported for other fungi (Yu and Keller 2005; Bayram et al. 2008), heterotrimeric G-proteins and MAPKs affect the production of *Trichoderma* antifungal metabolites (Reithner et al. 2005, 2007); and the *vell* velvet gene has also been implicated in the regulation of gliotoxin biosynthesis and other SMs genes, as well as conidiation in *T. virens* (Mukherjee and Kenerley 2010). Bioinformatics analysis of the three available *Trichoderma* genomes has revealed that the mycoparasitic species *T. atroviride* and *T. virens* are enriched in SMs-related genes as compared with *T. reesei*, a biomass-degrading species (Martinez et al. 2008; Kubicek et al. 2011; Baker et al. 2012; Mukherjee et al. 2012b). These latter and other recent studies have allowed progress in the field of *Trichoderma* SMs to determine the role of these compounds in three-way complex interactions between plants, phytopathogens, and *Trichoderma* (Viterbo et al. 2007; Velázquez-Robledo et al. 2011; Malmierca et al. 2012; Mukherjee et al. 2012b).

Hermosa et al. (2014) concluded that many SMs remain to be discovered in *Trichoderma* since this fungal genus includes multiple species that are highly adapted to different ecological niches and their SMs diversity seems to be limitless. Modifying growth conditions, manipulating regulatory factors, and using new mass spectrometry techniques should allow the discovery of novel molecules. Few SMs regulator proteins have been identified, and far from being a bottleneck, this has encouraged studies aimed at understanding SMs gene organization, transcription, and production. Many *Trichoderma* SMs isolated in the past were not investigated for a wide range of biological activity, and perhaps most of them need to be re-evaluated using new scenarios to explore novel applications. The development and use of acute, sensitive, and specific analytical methods would be fruitful in the screening of *Trichoderma* SMs, and for our understanding of their biosynthetic machinery in light of the expanding knowledge of microbial genetics and the information acquired from the genomes of this sequenced genus. However, the cooperation of scientists from several different disciplines is essential if we are interested in understanding the function of genes in SMs production. This may will lead to the discovery of novel compounds or pathways, which in turn may reveal important new aspects for many human applications, including pharmaceutical and agri-biotechnological uses.

A wide variety of SMs produced by *Trichoderma* was applied in agricultural, industrial, and pharmaceutical uses (Saravanakumar et al. 2015, 2018; El-Sharkawy et al. 2018; He et al. 2018). *Trichoderma* SMs exhibit diverse biological activities which enable their producers of *Trichoderma* spp., directly and indirectly, to perform multifunctional roles and prevail in different ecosystems. For example, fungi that inhabit the polar (Arctic and Antarctic) areas produce a variety of SMs in order to survive in the extreme and severe environmental conditions (Tripathi et al. 2018). Kamo et al. (2016) reported 11 known bioactive compounds in addition to another new one which produced by *T. polysporum* (OPU1571) isolated from Arctic region. However, production of these SMs is species- or in some cases strain-dependent and

may require special conditions and/or specific stimulator(s) (Zeilinger and Schuhmacher 2013). These SMs include terpenes, peptaibols, siderophores, pyrones, polyketides, gliotoxin, gliovirin, and isocyanate metabolites (Zeilinger et al. 2016). In this regard, more than 1000 of bioactive compounds have been reported to be produced by the members of *Trichoderma* genus (Neumann et al. 2015).

Biosynthesis of the SMs is controlled by gene clusters encoding a set of synthetic enzymes (such as nonribosomal peptide synthetases, polyketide synthases, and terpene synthases), accessory enzymes (such as oxidoreductases), and/or transporters and transcription factors (such as xylanase promoter-binding protein 1) (Bansal and Mukherjee 2016a, b; Derntl et al. 2017). Revealing of the whole genome sequence of some *Trichoderma* taxa, viz., *T. reesei*, *T. atroviride*, and *T. virens*, enriches the understanding about the SMs-related gene regulation (Druzhinina et al. 2011; Mukherjee et al. 2013). Nevertheless, most SMs' biosynthesis-related genes are silent under normal lab conditions which impedes the detection of new SMs (Wiemann and Keller 2014). To overcome this issue, use of SMs regulators is needed (Derntl et al. 2017).

*Trichoderma* spp. produce a variety of SMs for varied purposes which comprise competition, mycoparasitism, antibiosis against other microorganisms and predators, induction of microbial growth, communication with plant and other organisms, plant growth regulation, induction of plant resistance, protection against extreme environmental conditions, and as signaling or effectors molecules (Contreras-Cornejo et al. 2016; Venturi and Keel 2016; Abdalla et al. 2017; Saber et al. 2017; El-Sharkawy et al. 2018). However, some SMs pose toxic potentiality, while others have therapeutic and pharmaceutical uses (Vargas et al. 2014; Saravanakumar et al. 2016, 2018). In this chapter, we will discuss the recent progress on different SMs produced by members of genus *Trichoderma* for various purposes. Names and activities of some newly identified SMs are given in Table 12.1 with supporting references.

## 12.2 Antimicrobial Activity

Members of *Trichoderma* genus have been extensively studied as biocontrol agents against phytopathogens and pests due to their antagonistic potentialities (Liu et al. 2016; Kamo et al. 2016; Debbi et al. 2018). In this regard, El-Sharkawy et al. (2018) reported the biocontrol of wheat stem rust disease using isolates of *T. harzianum* HL1 and *T. viride* HL5. The anti-spore germination effect of their SMs (3-deoxy-d-mannonic acid, 5-hydroxymethylfurfural, succinic acid, 1,2,3-propanetriol monoacetate, 1,3-dihydroxyacetone, lactic acid, butanoic acid, and valeric acid) was recorded against the uredospores of *Puccinia graminis*. The antifungal activity of SMs of *T. harzianum* WKY1 against the mycelial growth and spore germination of *Colletotrichum sublineolum*, the causative of sorghum anthracnose, was also reported (Saber et al. 2017). Swain et al. (2018) reported a novel strain of *T.*

**Table 12.1** Newly identified secondary metabolites from *Trichoderma* spp

Activity	Compound name	Species name	Reference	
Antifungal	Nonribosomal peptides SF1	<i>T. velutinum</i>	Sharma et al. (2016b)	
	Nonribosomal peptides SF4	ACR-P1		
		1-(4-Bromobutyl)-2-piperidinone	<i>T. asperellum</i> GDfS1009	Wu et al. (2017)
		2,2,6,6-Tetramethyl-4-piperidinone		
		6-Pentyl-2H-pyran-2-one		
		2,6,10-Trimethyl-tetradecane		
		2,6,10-Trimethyl-pentadecane		
		Oxalic acid, butyl 6-ethyloct-3-yl ester		
		Trichokonin VI	<i>T. pseudokoningii</i> SMF2	Zhao et al. (2018)
		1, 2-Benzenedicarboxylic acid, bis (2-methylpropyl) ester	<i>T. longibrachiatum</i> T6	Zhang et al. (2018)
	1, 2-Benzenedicarboxylic acid, mono (2-ethylhexyl) ester			
	3-Deoxy-d-mannonic acid	<i>T. harzianum</i> HL1	El-Sharkawy et al. (2018)	
	5-Hydroxymethylfurfural			
	1,2,3-Propanetriol monoacetate			
	1,3-Dihydroxyacetone			
	Succinic acid			
	Valeric acid			
	Butanoic acid			
	Lactic acid			
Antibacterial	Trichaspside A	<i>T. asperellum</i> cf44-2	Song et al. (2018)	
	Trichaspside B			
	7,10-Epoxy cycloneran-3,11,12-triol			
	11-Hydroxy-9-harzien-3-one			
	Trichocitrin	<i>T. citrinoviride</i> cf-27	Liang et al. (2016b)	
	Nafuredin			
Citrostadienol				
	Citrinovirin			

(continued)

**Table 12.1** (continued)

Activity	Compound name	Species name	Reference
Precursors for antimicrobial compounds	Acetamide	<i>T. asperellum</i> GDFS1009	Wu et al. (2017)
	Diethylamine		
	Ethylene glycol		
	Ethanolamine		
	o-Toluic acid		
	Ethylamine		
	Glycine		
Cytotoxic	Tandyukisins E	<i>T. harzianum</i>	Suzue et al. (2016)
	Tandyukisins F	OUPS-111D-4	
Anticancer	16-Methylheptadecanoic acid methyl ester	<i>Hypocrea lixii</i> TSK8	Saravanakumar et al. (2015)
Antioxidant	Hydrophobin HFBII	<i>T. reesei</i>	Khalesi et al. (2016)
Antihypercholesterolemic	Lovastatin	<i>T. viride</i>	Rashid et al. (2014)
Mycotoxin, mutagenic, fetotoxic, teratogenic	Alternariol 1'-hydroxy-9-methyl ether (1)	<i>Trichoderma</i> sp. Jing-8	Solhaug et al. (2015)
Mycotoxin, antimalarial, anticancer	Gliotoxin	<i>T. virens</i>	Vargas et al. (2014)
Mycotoxin	Trichothecene (trichodermin)	<i>T. arundinaceum</i>	Shentu et al. (2013)
		<i>T. brevicompactum</i>	
Plant growth promoter	Indole-3-acetic acid	<i>T. harzianum</i> WKY1	Saber et al. (2017)
	Chrysophanol	<i>T. harzianum</i> ETS-323	Liu et al. (2016)
	Ethylene	<i>T. atroviride</i>	Contreras-Cornejo et al. (2015)
	Harzianolide	<i>T. harzianum</i> SQR-T037	Cai et al. (2013)
	$\beta$ -Acoradiene	<i>T. aggressivum</i>	Lee et al. (2016)
	$\beta$ -Cubebene	<i>T. asperellum</i>	
	$\beta$ -Cedrene	<i>T. harzianum</i>	
	$\beta$ -Bisabolene	<i>T. longibrachiatum</i>	
	$\beta$ -Himachalene	<i>T. pseudokoningii</i>	
	$\gamma$ -Himachalene	<i>T. viride</i>	
Coconut aroma	Aroma6-pentyl- $\alpha$ -pyrone	<i>T. viride</i> EMCC-107	Fadel et al. (2015)
Aroma compound	$\delta$ -Octalactone		
	$\gamma$ -Nonalactone		
	$\gamma$ -Undecalactone		
	$\gamma$ -Dodecalactone		
	$\delta$ -Dodecalactone		

(continued)

**Table 12.1** (continued)

Activity	Compound name	Species name	Reference
Antiplatelet aggregation	Herquiline B	<i>T. pinophilus</i> F36CF	Vinale et al. (2017)
Antiproliferative	O-Methylfunicone		
	Harziaphilic acid	<i>T. harzianum</i> M10	Vinale et al. (2012)
Siderophore	Ferrirubin Ferricrocin Coprogen B Dimerumic acid		

*erinaceum* isolated from tree barks in India as a biocontrol and biofertilizer agent for rice crop. This isolate significantly inhibited growth of the phytopathogenic fungi *Rhizoctonia solani*, *Sclerotium rolfsii*, and *S. oryzae* in vitro and *R. solani* and *Helminthosporium oryzae* under field conditions. A novel isolate of *T. asperellum*, designated GDFS1009, shows potent antifungal activity against the phytopathogens *Fusarium oxysporum* f. sp. *cucumerinum* Owen and *F. graminearum*; the causal agents of *Fusarium* wilt of cucumber and stalk rot of corn, respectively, was also reported by Wu et al. (2017). This isolate exhibited high inhibition rate against both of the two pathogens in vitro and in the greenhouse. In addition, precursors for antimicrobial compounds such as acetamide, diethylamine, ethylene glycol, ethanolamine, o-toluic acid, ethylamine, and glycine, as well as a set of antimicrobial SMs such as 1-(4-bromobutyl)-2-piperidinone, 2,2,6,6-tetramethyl-4-piperidinone, 6-pentyl-2H-pyran-2-one, 2,6,10-trimethyl-tetradecane, 2,6,10-trimethyl-pentadecane, and oxalic acid, butyl 6-ethyloct-3-ylester were reported to be produced by *T. asperellum* GDFS1009. Molecularly, in the *T. asperellum* GDFS1009 genome, genes encoding for mycoparasitism-related enzymes (chitinase, glucanase, and protease) and induced resistance elicitors (endopolygalacturonase, Epl protein, hydrophobin, polygalacturonase, swollenin, and xylanase) were detected. All of these detected factors are contributed in the antagonistic nature of *T. asperellum* GDFS1009 against the two tested *Fusarium* pathogens. In general, the antagonistic mechanisms exerted by *Trichoderma* members include production of antimicrobial SMs (antibiosis), mycoparasitism, competition with other microorganisms for space or nutrients, and/or induction of the plant resistance against the invaded pathogen (Abdel-Fattah et al. 2007; Qualhato et al. 2013; Sadykova et al. 2015; Arseneault and Fillion 2017; Zhang et al. 2018).

On the other hand, development of multidrug-resistant pathogens as a result of the inadvisable use of antibiotics and different climatic changes increases the demand to discover novel antimicrobial SMs (Garcia-Solache and Casadevall 2010; Chaudhary 2016). Biomedical activities of SMs produced by *Trichoderma* spp. have been studied in the recent years as new alternatives to the common antibiotics (Sadykova et al. 2015; Saravanakumar et al. 2018). Various new SMs with antimicrobial activities have been identified from *Trichoderma* spp. Nonribosomal peptides (NRPs) are a group of antimicrobial peptides produced by a wide range of

microorganisms, among them, the so-called peptaibiotics which produced mainly by *Trichoderma* spp. More than 1297 peptaibiotic sequences have been reported in the literature (Neumann et al. 2015). The produced NRPs showed a variety of bioactivities including antifungal, antibacterial, antiviral, anticancer, antiparasitic, and immunosuppressant (Panizel et al. 2013; Zhao et al. 2018). In addition, they have been used as bioagents against phytopathogenic fungi (Degenkolb et al. 2015). In this regard, two NRPs, belonging to subfamilies SF4 (medium chain of amino acid residues) and SF1 (long-chain amino acid residues), were reported to be produced by the new psychrotrophic isolate *T. velutinum* ACR-P1 (Sharma et al. 2016b). This isolate showed an aggressive antifungal activity in vitro against the phytopathogenic fungi *F. oxysporum*, *Verticillium dahliae*, *Alternaria alternata*, and *Colletotrichum capsici* (Sharma et al. 2017). Zhao et al. (2018) reported another antimicrobial peptaibol, trichokonin VI, produced by *T. pseudokoningii* SMF2. This peptaibol exhibited antifungal activity against the gray mold of moth orchid caused by *Botrytis cinerea*. Eight new peptaibols belonging to the trichorzianine family were also isolated from the sponge-associated isolate of *T. atroviride* NF16 (Panizel et al. 2013). The isolated peptaibols showed moderate antibacterial activity. Zhang et al. (2018) identified four inhibitory SMs from the culture filtrate of *T. longibrachiatum* T6. Of them, two compounds (1,2-benzenedicarboxylic acid, bis(2-methylpropyl) ester and 1,2-benzenedicarboxylic acid, mono(2-ethylhexyl) ester) showed highly fungicidal activity against *Valsa mali*, the causal agent of valsa canker of apple, at 200  $\mu\text{g mL}^{-1}$ . Moreover, *Trichoderma* spp. play an important role in inhibiting mycotoxin-producing fungi and reducing their toxin biosynthesis. Consumption of the mycotoxin-contaminant foods results in many health issues; sometimes it may be carcinogenic for humans and animals. Braun et al. (2018) reported an antifungal (mycoparasitic) activity of *T. harzianum* MRI349 against the mycotoxin-producing fungi *Aspergillus carbonarius* and *A. flavus* and inhibition of their mycotoxin biosynthesis at the transcriptional level. The venomous effects of members of *Fusarium* genus are attributed to their production of mycotoxins which cause dangerous health issues such as fumonisins, produced by *F. moniliforme*, which cause neurotoxicity, leukoencephalomalacia, hepatotoxicity, and liver cancer (Antonissen et al. 2014).

Fumonisin B1 toxin (FB1) is a well-known inhibitor of sphingolipid biosynthesis through inhibiting ceramide synthase (CS) enzyme (Heidtmann-Bemvenuti et al. 2011). In a recent study, Sharma et al. (2018) indicated that FB1 inhibited CS in yeast (*Saccharomyces cerevisiae*) but not in *T. guizhouense*. FB1 has been found to compete the substrate for the binding sites of the CS resulting in an inactive state of the enzyme. However, in case of CS from *T. guizhouense*, no competition for the substrate binding site was observed.

New bioactive SMs have been reported also from marine-derived *Trichoderma* spp. including peptides, terpenes, aromatics, and polyketides (Zhu et al. 2015; Zhang et al. 2017a; Blunt et al. 2017). Song et al. (2018) identified ten terpenes from the culture filtrate of the *T. asperellum* cf44-2, an endophytic fungus of the marine alga *Sargassum* sp. Of the isolated SMs, trichaspin, trichaspsides A and B (bisabolane derivatives); 9-cycloneren-3,7,11-triol, 11-cycloneren-3,7,10-triol, and 7,10-epoxycycloneran-3,11,12-triol (cyclonerane sesquiterpenes); and



11-hydroxy-9-harzien-3-one (harziane diterpene) were identified. Four SMs of them exhibited antibacterial activity against five aquatic pathogenic bacteria (*Vibrio parahaemolyticus*, *V. anguillarum*, *V. harveyi*, *V. splendidus*, and *Pseudoalteromonas citrea*). Trichocitrin, a new antibacterial diterpene, was also extracted from the culture of *T. citrinoviride* cf-27, an endophyte of the marine brown alga (Liang et al. 2016b). In addition, another four known SMs (nafuredin, 5-hydroxy-2,3-dimethyl-7-methoxychromone, 24-methylenecycloartanol, and citrostadienol) were also produced by *T. citrinoviride* cf-27. Of them, citrostadienol and nafuredin showed antibacterial potentiality against *Escherichia coli*. Citrinovirin, a novel norditerpene, was isolated and identified from the culture of *T. citrinoviride* cf-27 in addition to cyclonerodiol, 3-(2-hydroxypropyl)-4-(hexa-2E,4E-dien-6-yl) furan-2(5H)-one, and 5-hydroxy-3-hydroxymethyl-2-methyl-7-methoxychromone (Liang et al. 2016b). Citrinovirin exhibited antibacterial activity against the pathogenic bacteria *Staphylococcus aureus* and a biotoxicity against the marine zooplankton *Artemia salina* and the phytoplankton *Chattonella marina*, *Heterosigma akashiwo*, and *Prorocentrum donghaiense* (Liang et al. 2016a). On the other hand, trichodiene, non-phytotoxic volatile organic compound produced by two isolates of *T. harzianum* (T34-5.27 and E20-5.7), exhibited a negative effect on the biocontrol activity against the common bean insect pest *Acanthoscelides obtectus*. Application of the trichodiene producer isolates led to an increment in the daily insect emergence and increased the attraction capacity of insects more than their parental strains on the treated bean plants (Rodríguez-González et al. 2018).

### 12.3 Therapeutic Activity

Various SMs produced by *Trichoderma* spp. have shown eminent therapeutic potency against different human diseases. Tandyukisins E and F, new decalin derivatives produced by *T. harzianum* OUPS-111D-4, showed cytotoxic activity against the cancer cell lines P388, HL-60, and L1210 (Suzue et al. 2016). In addition, 16-methylheptadecanoic acid methyl ester produced by the marine *Trichoderma* (*Hypocrea lixii* TSK8) exhibited a significant anticancer activity against two human cancer cell lines: oral cancer (KB) and skin carcinoma (A431). The inhibitory concentrations against KB and A431 cancer cells were  $18.75 \pm 0.12$  and  $37.5 \pm 0.42$  mg mL<sup>-1</sup>, respectively (Saravanakumar et al. 2015). Class II hydrophobin (HFBII) is another bioactive compound produced by *T. reesei* and poses antioxidant and ACE (angiotensin I-converting enzyme)-inhibitory activities. Their ACE-inhibitory activity was reported at  $\geq 0.5$  mg mL<sup>-1</sup>, while their antioxidant activity at 0.01–0.40 mg mL<sup>-1</sup> (Khalesi et al. 2016). Cariaco et al. (2018) reported the immunomodulatory and antimalarial effect of the ethanolic extract of the culture filtrate produced by the isolate *T. stromaticum* against *Plasmodium falciparum* NF54 in infected human red blood cells and in a mouse model of experimental cerebral malaria. One of the various therapeutic benefits of SMs produced by *Trichoderma* spp. is their role as a cholesterol-lowering agent (e.g., lovastatin and compactin). Lovastatin is an anti-hypercholesterolemic drug (a competitive

inhibitor of hydroxy-methylglutaryl-CoA reductase, the first enzyme in the cholesterol biosynthesis). Of 17 fungal isolates screened for lovastatin production, Rashid et al. (2014) reported a great capability for its production ( $72.9 \mu\text{g g}^{-1}$ ) by *T. viride*.

On the other hand, some SMs produced by *Trichoderma* spp. are hazardous to human health such as mycotoxins. In this regard, Zhang et al. (2017b) isolated a novel natural mycotoxin from culture filtrate of *Trichoderma* sp. Jing-8 which was identified as alternariol 1'-hydroxy-9-methyl ether (1). This mycotoxin may show mutagenic, fetotoxic, teratogenic characteristics or results in DNA damage (Solhaug et al. 2015). One of the most important epidithiodioxopiperazine-type mycotoxins produced by *Trichoderma* spp. is gliotoxin (GT). It was isolated as a secondary metabolite of *T. virens* (Vargas et al. 2014). In spite of the widely use of GT-producing *T. virens* isolates in agriculture as biocontrol agents, GT production has been reported during infection with *A. fumigatus* (aspergillosis) in human lungs and sera, and in mice. Moreover, it is considered as a virulence determinant of this pathogen. GT contributes to the infection process by suppressing the activity of immune cells (neutrophils) or phagocytes (Scharf et al. 2016). Recent studies suggest the use of GT as a diagnostic biomarker for aspergillosis infection in neutropenic patients (Sugui et al. 2017). However, at concentrations below the cytotoxicity level, GT may have some therapeutic uses such as antimalarial and anticancer drug (Hubmann et al. 2017, 2018). Trichothecene (trichodermin) is another sesquiterpenoid mycotoxin produced by *T. arundinaceum* and *T. brevicompactum*. It may be naturally accumulated at potentially harmful concentrations in cereals and grains (Shentu et al. 2013; Sharma et al. 2016a). Their modes of action include inhibition of protein synthesis in the 60S ribosomal subunit and in mitochondria, production of free radicals which cause oxidative stress, induction of ribotoxic stress, cell proliferation, and cytotoxicity responses in animal cells (Sharma et al. 2016a).

## 12.4 Plant Growth Promotional Activity

Numerous plant growth promoters have been reported to be produced by members of genus *Trichoderma* (Zeilinger et al. 2016). Saber et al. (2017) reported a high production ( $138.9 \mu\text{g mL}^{-1}$ ) of the phytohormone indole-3-acetic acid (IAA) by the isolate *T. harzianum* WKY1 which improved the plant growth of sorghum. Chrysophanol is another anthraquinone secondary metabolite produced by *T. harzianum* ETS-323 which significantly stimulated the growth of cabbage seedlings and induced the production of the photosynthesis-related proteins in their leaves. In addition, the sucrose transport-related genes were overexpressed in the chrysophanol-treated cabbage leaves (Liu et al. 2016). In another study, the plant hormone ethylene produced by *T. atroviride* was found to be involved in the root system alterations (root architecture and biomass) in *Arabidopsis* seedlings. It affected auxin signaling through the central regulator CTR1 and enhanced activity of mitogen-activated protein kinase 6 (Contreras-Cornejo et al. 2015). More recently, the plant growth-promoting activity of the endophytic fungi has received special attention. The growth-promoting mechanisms include enhancement of

1-aminocyclopropane-1-carboxylic acid (ethylene precursor) or production of plant hormones such as IAA, gibberellins, auxins, and cytokinins (Patle et al. 2018). In this regard, the endophytic fungus *T. gamsii* NFCCI 2177, isolated from lentil roots in the Indian Himalayan Region, was found to pose a potential growth-promoting activity on maize, soybean, wheat, and lentil. Moreover, it showed phosphate-solubilizing capacity and ammonia production ability (Rinu et al. 2014). Martínez-Medina et al. (2014) studied the inducing effects of *T. harzianum*, *T. ghanense*, and *T. hamatum* on the phytohormone profile with plant growth-promoting potential (zeatin, zeatin riboside, indole-3-acetic acid, 1-aminocyclopropane-1-carboxylic acid, and abscisic acid) on melon plants. An induction in auxin and reduction in cytokinins and abscisic acid content were recorded. The study showed a great association of auxin trigger with plant growth improvement by *Trichoderma*. In contrast, in another study, the non-hormone-producing isolate *T. harzianum* T-22 (in axenic growing media) enhanced the plant growth by regulating hormone biosynthesis genes in the *Prunus* rootstock (Sofa et al. 2012). Harzianolide is another recently identified SM from *T. harzianum* strain SQR-T037 which poses a remarkable plant growth-promoting activity. Treatment of tomato seedlings with harzianolide as purified compound or in the crude extract significantly enhanced their growth by 2.5-fold. In addition, it exhibited a systemic resistance inducing activity against phytopathogenic fungi (Cai et al. 2013). In a recent study, of 20 *Trichoderma* isolates screened for volatile-mediated plant growth promotion activity, 9 isolates belonging to *T. aggressivum*, *T. asperellum*, *T. harzianum*, *T. longibrachiatum*, *T. pseudokoningii*, and *T. viride* significantly enhanced overall plant growth and total chlorophyll content in *Arabidopsis thaliana*. A total of 141 unique volatile compounds were identified including hydrocarbons, alcohols, ketones, aldehydes, alkanes, alkenes, esters, aromatic compounds, heterocyclic compounds, and various terpenes. Moreover, plant growth-promoting isolates were found to produce terpenes such as  $\beta$ -acoradiene,  $\beta$ -cubebene,  $\beta$ -cedrene,  $\beta$ -bisabolene,  $\beta$ -himachalene, and  $\gamma$ -himachalene (Lee et al. 2016).

On the other hand, *Trichoderma* spp. play another crucial indirect role in enhancing plant growth through alleviating ecological stresses leading for crop yield improvement. Zaidi et al. (2018) reported that application of *T. harzianum* strain S2 in addition to the best management practices of International Rice Research Institute enhanced the grain yield of rice under rainfed conditions, recording 4.91 and 4.81 t ha<sup>-1</sup> during 2013 and 2014, respectively. Role of *Trichoderma* spp. in mitigating salinity stress on crop plants was also studied. Yasmeen and Siddiqui (2017) reported that seedlings of rice and maize treated with the endophytic fungus *T. harzianum* (Th-6) and grown under salinity conditions (50, 100, and 150 mM NaCl) exhibited better growth and higher relative water content and stomatal conductance compared to the Th-6-untreated plants. In addition, the Th-6-treated seedlings showed higher content of the photosynthetic pigments, proline content, and higher activity of catalase and superoxide dismutase enzymes. Moreover, in a recent study, it was found that the root

exudates from tomato plants exposed to different stress factors acted as chemoattractants of the soil fungus *T. harzianum* T-22 (Lombardi et al. 2018).

Solubilization of sparingly soluble minerals is another mechanism by which *Trichoderma* spp. may promote plant growth (enhance nutrient uptake) through production of mineral-solubilizing metabolites such as organic acids (acidification), siderophores (chelation), ferric reductase (redox), and phytase (hydrolysis). Li et al. (2015) reported the isolate *T. harzianum* SQR-T037 as a mineral-solubilizing fungus with the ability to solubilize phytate,  $\text{Fe}_2\text{O}_3$ ,  $\text{CuO}$ , and metallic Zn as well as produce organic acids such as lactic acid, citric acid, tartaric acid, and succinic acid.

## 12.5 Biotechnological Activity

A lot of studies that address the biotechnological applications using members of *Trichoderma* genus have been done in the last few years. One of the most interesting applications in this field is the green synthesis of metallic nanoparticles based on *Trichoderma* species which provides an eco-friendly, economic, effective, and low-energy method for nanoparticle production. Their capability to produce various types of SMs and enzymes makes them good candidates for biosynthesis of metallic nanoparticles. These SMs such as peptaibols, siderophores, polyketides, terpenoids/steroids, nonribosomal peptides, and pyrones contain many phenolic groups that have been oxidized and convert to quinones donating electrons which act as reducing and stabilizing agents through the biosynthesis process (Mukherjee et al. 2012a). Qu et al. (2017) reported a success biosynthesis of gold nanoparticles of diverse shapes using the biomass of the newly isolated strain *Trichoderma* sp. WL-Go. These biogenic nanoparticles have a significant potential for decolorization of different azo dyes. In this regard, different species of *Trichoderma* were used also in the biosynthesis of gold nanoparticles of various sizes and shapes such as *T. asperellum* (Mukherjee et al. 2012a), *T. harzianum* (Tripathi et al. 2014), and *T. viride* (Mishra et al. 2014). Silver nanoparticles were also biosynthesized using *T. harzianum* (Guilger et al. 2017). The produced silver nanoparticles exhibited a strong antifungal activity against mycelial growth and sclerotia germination of the white mold fungus *Sclerotinia sclerotiorum*, which attack many crops. Silver nanoparticles were biosynthesized also using *T. longibrachiatum*, *T. harzianum*, and *T. viride* and showed significant inhibitory effect against the fungal growth of the phytopathogenic fungi: *F. verticillioides*, *F. moniliforme*, *Penicillium brevicompactum*, *H. oryzae*, and *Pyricularia grisea* (Elamawi et al. 2018). Saravanakumar and Wang (2018) reported also a biosynthesis process of silver nanoparticles of size ranged between 15 and 25 nm using *T. atroviride* which showed antibacterial, antioxidant, and cytotoxicity activities. In another study, selenium nanoparticles were also biosynthesized using culture filtrate, cell lysate, and crude cell wall of *T. asperellum*, *T. harzianum*, *T. atroviride*, *T. virens*, *T. longibrachiatum*, and *T. brevicompactum* producing nanoparticles of size ranged between 49.5 and 312.5 nm (Nandini et al. 2017). The biosynthesized selenium nanoparticles inhibited growth, sporulation,

and zoospore viability of the pearl millet downy mildew fungus (*Sclerospora graminicola*).

Moreover, *Trichoderma* spp. have another interesting biotechnological application represented in their capability to degrade the highly toxic, mutagenic, and carcinogenic azo dyes produced from textile, food, plastic, printing, leather, and cosmetic industries and disposed into the ecosystem as wastewater. A noteworthy degradation, up to an efficiency of 99.2%, of azo dyes in the real textile effluent using *T. tomentosum* under non-sterile conditions was reported (He et al. 2018). Remarkable enzymatic activities of manganese peroxidase and lignin peroxidase were recorded during the azo dye decolorization process revealing their possible involvement in this process.

One of the most important biotechnological applications of *Trichoderma* spp. is their role as potential bioremediators in the eco-friendly metal removal technology. Their strategies in this regard can be categorized into four groups: biosorption, bioaccumulation, biovolatilization, and phytobial remediation (Tripathi et al. 2013). Recent researches showed a remarkable metal tolerance as well as a high capacity to accumulate these metals from the surrounding polluted environment by *Trichoderma* spp. Some isolates of *Trichoderma* spp. pose multiple tolerances to more of one kind of heavy metals. Their tolerant responses may differ in case of single than multiple metal ions; synergistic or antagonist interactions may take place between these metal ions (Siddiquee et al. 2015). In this regard, Nongmaithem et al. (2016) screened 14 *Trichoderma* isolates for their biosorption potential of nickel and cadmium through metabolically mediated pathways of uptake. Of the evaluated isolates, three (MT-4, UBT-18, and IBT-I) showed a high potential of nickel tolerance (up to 200 ppm), and three (MT-4, UBT-18, and IBT-II) exhibited a significant tolerance of cadmium (up to 150 ppm). Total removal of nickel was observed at concentrations up to 40 ppm. The biosorption activity of an organism is attributed to the ion-exchange capacity of their SMs which contain functional groups such as hydroxyls, carbonyls, carboxyls, sulfonates, amides, imidazoles, phosphonates, and phosphodiester (Pradhan et al. 2007). Many of these functional groups exist in SMs produced by *Trichoderma* spp. Biovolatilization is another alternative strategy exerted by *Trichoderma* spp. in the metal bioremoval technology. This strategy includes an enzymatic transformation of the metalloid compounds into their volatile derivatives (i.e., biomethylation). With regard to this, three mercury-resistant isolates of *T. virens*, isolated from the San Joaquin region in the State of Querétaro, México, were found to grow at high  $\text{HgCl}_2$  levels ranged between 100 and 200  $\text{mg L}^{-1}$  and catalyze mercury volatilization and accumulation. Of them, *T. virens* strain 20-D exhibited the highest Hg volatilization potential (213.04  $\mu\text{g m}^{-3}$ ), while their mycelium accumulation of mercury was 18.5  $\mu\text{g g}^{-1}$ . Interestingly, inoculation of  $\text{HgCl}_2$ -treated *A. thaliana* plants with these isolates significantly reduced Hg concentration in their roots and rosette leaf tissues recording 75% and 50% reduction, respectively (Hernández-Flores et al. 2018). Moreover, the bioremediation role of *Trichoderma* spp. extends also to their biodegradation potential for organic contaminants. Andreolli et al. (2016) isolated a fungal isolate (*T. longibrachiatum* Evx1) which has the ability to degrade diesel fuel and polycyclic aromatic

hydrocarbons as well as decolorize polynuclear organic dyes. Their biodegradation potential for the C12–40 hydrocarbons reached 54.2%.

Production of aroma compounds as natural food additives or flavors is another important industrial application of *Trichoderma* spp. Various studies have reported production of SMs by *Trichoderma* species such as the unsaturated lactone 6-pentyl- $\alpha$ -pyrone, the volatile compound responsible for the coconut-like aroma in their cultures. In this regard, Fadel et al. (2015) reported the production of coconut aroma 6-pentyl- $\alpha$ -pyrone as a major volatile compound in addition to  $\delta$ -octalactone,  $\gamma$ -nonalactone,  $\gamma$ -undecalactone,  $\gamma$ -dodecalactone, and  $\delta$ -dodecalactone by *T. viride* EMCC-107 cultivated as a solid-state fermentation using sugarcane bagasse. The produced coconut aroma was characterized and evaluated for its impact on the overall odor profile. Microbial aromatic compounds were also produced by *T. viride* using solid-state fermentation of *Pandanus tectorius* fruits as a substrate. Using GC/MS system, 27 aromatic compounds were detected in the culture filtrate including alkene hydrocarbons, alcohol, amide, and monoterpene aldehyd (Darmasiwi et al. 2016).

## 12.6 Microbial Communications

Root microbiome refers to various microbial communities surrounding and inhabiting the plant roots. Different bidirectional interactions occur between these microbial communities with each other in the soil, i.e., antagonism or synergism on one side and between them and the plant roots on the other side. Effect of root microbiome on the plant is ranging from enhancing their health, development, and stress tolerance to parasitizing their roots. In the same time, growth of root microbiome is positively or negatively affected by the root exudates. Moreover, some researchers consider the root microbiome as a secondary genome which provides the plant with microbial SMs (Rout and Southworth 2013). The high species diversity and richness in the root microbiome result in intra- and interspecies communications between their members. SMs play the key role in implementing these communications as chemical signals. In spite of the large number of SMs produced by these microorganisms, little are known about their activities and biosynthesis. Moreover, genome mining of a single organism shows an inconsistency between the number of the genes involved in the secondary metabolism and the known SMs (Crane et al. 2013). Interestingly, recent researches showed that the interspecies communication between microbiome members may result in inducing silent gene clusters to produce novel SMs by other species (Netzker et al. 2015). Many researchers have studied co-cultivations of two or more organisms in order to trace novel SMs (Bertrand et al. 2014; Marmann et al. 2014). In this regard, harziaphilic acid, a novel SM, with antiproliferative effect on colorectal carcinoma cells, was isolated and fully characterized from the fungal co-culturing of *T. harzianum* M10 (producer) and the endophyte *Talaromyces pinophilus* F36CF (elicitor). Furthermore, upregulation of siderophores (ferrirubin, ferricrocin, coprogen B, and dimerumic acid) for both

fungi was also reported in this mixed culture. Production of microbial siderophores in the soil has a growth-promoting effect on the plants (iron solubilization), while it has a suppressive effect on other soil microorganisms (iron competition) (Vinale et al. 2012). On the contrary, biosynthesis of 3-O-methylfunicone and herquiline B by *T. pinophilus* F36CF was downregulated in the presence of *T. harzianum* M10 compared with the single culture (Vinale et al. 2017). In a recent study, co-culturing of *T. hamatum* (CMB-MF030) and *Chaunopycnis* sp. (CMB-MF028) led to production of chaunopyran A, a rare class of 2-alkenyl-tetrahydropyran, through activation of the silent gene clusters encoding for it. In addition, this mixed culturing resulted also in methylation of pyridoxatin (antifungal agent) converting it to its non-antifungal form (Shang et al. 2017). Wu et al. (2018) reported also enhancement of specific amino acid production as well as antimicrobial compounds from the mixed culture of *Bacillus amyloliquefaciens* ACCC11060 and *T. asperellum* GDFS1009 compared with their single cultures. Co-culturing of a microorganism and plant was also reported. In this regard, co-cultivation of *A. thaliana* seedlings with *T. virens* Tv29.8 and *T. atroviride* IMI 206040 significantly promoted the overall plant growth specially the lateral roots and root hairs through IAA production in both normal and saline conditions (Contreras-Cornejo et al. 2014). Triggering of abscisic acid, L-proline, and ascorbic acid and enhanced elimination of Na<sup>+</sup> through root exudates was also reported for the co-cultivated seedlings. In contrast, in an axenic co-culture of the two isolates *T. harzianum* T-22 and BOL-12QD with the *Chenopodium quinoa* cv. Kurmi and Maniqueña real, a significant inhibitory effect by the two isolates was recorded on the plant growth, specially the lateral root development, as well as chlorophyll and betalain contents (Rollano-Peñaloza et al. 2018). In another study, volatile SMs produced by *T. asperellum* IsmT5 (6-pentyl- $\alpha$ -pyrone) negatively affected the plant growth of *A. thaliana* inhibiting primary root, leaf size, and fresh weight (Kottb et al. 2015). In axenic cultures, nature of the *Trichoderma*-plant interactions depends on the compatibility between the *Trichoderma* strains and the plant genotypes.

## 12.7 Conclusions and Outlook

Numerous bioactive SMs, produced by members of genus *Trichoderma*, have been discovered each year which have different agricultural, biotechnological, and therapeutic applications in our life. In spite of the immense ability of *Trichoderma* spp. to produce these SMs, our knowledge about their biosynthesis, regulating genes, bioactivities, and elicitors is still limited. Genome mining of members of genus *Trichoderma* is essential to improve our understanding for their obscure secondary metabolism, help in discovery of new SMs, and generate mutant strains with massive capacity to produce biotechnologically and therapeutically important SMs. Molecular studying of the bidirectional *Trichoderma*-plant communications and their signaling molecules is emerging also as an essential need for the best field exploitation of these beneficial fungi. Furthermore, accelerated technical progress

at molecular level in the identification and biodiversity studying tools will lead to the discovery of novel species of genus *Trichoderma*.

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