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REVIEW

Secondary metabolites of endophytic *Xylaria* species with potential applications in medicine and agriculture

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Abstract Fungal endophytes are important sources of bioactive secondary metabolites. The genus *Xylaria* Hill (ex Schrank, 1789, Xylariaceae) comprises various endophytic species associated to both vascular and non vascular plants. The secondary metabolites produced by *Xylaria* species include a variety of volatile and non-volatile compounds. Examples of the former are sesquiterpenoids, esters, and alcohols, among others; and of the latter we find terpenoids, cytochalasins, mellein, alkaloids, polyketides, and aromatic compounds. Some of these metabolites have shown potential activity as herbicides, fungicides, and insecticides; others possess antibacterial, antimalarial, and antifungal activities, or α-glucosidase inhibitory activity. Thus metabolites from *Xylaria* are promising compounds for applications in agriculture for plague control as biopesticides, and biocontrol agents; and in medicine, for example as drugs for the treatment of infectious and non-infectious diseases. This review seeks to show the great value of the secondary metabolites of *Xylaria*, particularly in the agriculture and medicine fields.

Keywords Endophytic fungus · *Xylaria* · Secondary metabolites · Bioactive compounds · Drug and agrochemical application

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Introduction

The order Xylariales comprises nearly 800 species in eight families, the most important of which is the Xylariaceae; it includes the genus *Xylaria* with over 100 species. *Xylaria* species are commonly found as saprophytes and endophytes (Webster and Weber 2007).

Fungal endophytes are found inside the living tissues of all plants and grow without causing apparent damage or disease in the host plant. These fungi are symbionts that can protect their host by producing enzymes or secondary metabolites that directly inhibit the action of microbial pathogens, plants growing around and animals; they can also protect them by inducing the host to synthesize secondary metabolites, or enzymes, that improve their defenses against pathogens and hervibores; moreover, they can occupy a niche in the plant tissues and hamper the colonization and infection by harmful microorganisms (Gao et al. 2010; Guzmán-Trampe et al. 2015).

Xylaria species are dominant, fast growing and generalist endophytes found in tropical plants (Arnold and Lutzoni 2007; Hyde and Soytong 2008). They have been isolated from vascular plants (conifers, monocots, dicots, ferns, and lycopsids) and from nonvascular plants (liverworts); (Davis et al. 2003). They produce secondary metabolites which are chemically diverse and biologically active (Song et al. 2014).

Endophytic fungi synthesize various bioactive secondary metabolites that may directly or indirectly be used as therapeutic agents or as biopesticides (Kusari et al. 2012; Guzmán-Trampe et al. 2015). The chemical diversity of secondary metabolites produced by *Xylaria* species includes terpenoids, suchs as eudesmanes and guaianes; cytochalasins, mellein, alkaloids, polyketides, and aromatic compounds; and volatile organic compounds (VOCs),

including sesquiterpenoids, esters, and alcohols, among others (Song et al. 2014; Sánchez-Ortiz et al. 2016). The production of these bioactive secondary metabolites is characteristic of many mutualistic endophytes and favors the symbiosis in the host plant (Davis et al. 2003).

A comprehensive review about *Xylaria* was published in Song et al. (2014), it encompasses the secondary metabolites produced by species isolated not only as endophytes but also from different substrates, and their biological activities reported until 2012. In this review, we update this information by summing up recently reported secondary metabolites from endophytic species, with potential use in medicine and agriculture, according to their biological activity.

Medicinal potential

Antimicrobial agents

Five antimicrobial compounds were isolated from *Xylaria* sp. SNB-GTC2501, an endophyte of *Bisboecklera microcephala* gathered in French Guiana. The compounds include two new isopimarane diterpenoids, xylabisboein A (**1**) and B (**2**), and the three known compounds (−)-5-methylmellein (**3**), mellein-5-carboxylic acid or 5-carboxylmellein (**4**) and ergosterol peroxide (**5**). The minimal inhibitory concentration (MIC) values against *Staphylococcus aureus*, *Trichophyton rubrum* and *Candida albicans* were higher than 128 μg/mL for all the compounds (Sorres et al. 2015). Moreover, Chinworrungsee et al. (2001) demonstrated that 5-carboxylmellein (**4**) presents antimalarial activity against a multidrug resistant strain of *Plasmodium falciparum* K1 with an IC_{50} value of 4 μg/mL.

Xylaria sp. Acra L38, an endophyte isolated from *Aquilaria crassna*, a plant that grows in Thailand, produces zofimarin (**6**) (Chaichanan et al. 2014). Compound **6** is a selective antifungal with activity against *C. albicans*, including azole-resistant strains, *Saccharomyces cerevisiae*, *Cryptococcus neoformans*, and *Aspergillus* sp. It is important to note that zofimarin (**6**) was previously identified from a marine fungus, *Zopfielle marina* SANK21274, in 1987 and patented (Ogita et al. 1987; Vicente et al. 2003; Chaichanan et al. 2014). In addition, Chaichanan et al. (2014) optimized the fermentation medium for the production of the compound **6** and found that it was only produced when Czapek yeast extract culture medium was used and that sucrose, maltose, glucose and $NaNO_3$ were important components for its production.

Xylaria sp., isolated from the orchid *Anoectochilus setaceus* from Sri Lanka, produces the antimicrobial helvolic acid (**7**). The nortriterpenoid **7** showed antibacterial activity against the Gram-positive bacteria *Bacillus subtilis* and methicillin-resistant *S. aureus* (MRSA) with MIC values of 2 and 4 μg/mL, respectively (Ratnaweera et al. 2014).

The compound 4-cyanomethoxy benzoic acid (**8**) was isolated from *Xylaria* sp. strain FPLX-10, an endophyte of *Ficus pumila* Linn. collected in India, by using a dereplication strategy (Rakshith et al. 2013). This compound was also identified from the Indonesian marine endophytic fungus *Xylaria psidii* KT30, isolated from the red alga *Kappaphycus alvarezii* (Tarman et al. 2011). Compound **8** showed antibacterial activity against *Escherichia coli*, *Vibrio parahaemolyticus*, *S. aureus* and *Listeria monocytogenes* and antifungal activity on *C. albicans* and *Aspergillus niger* in TLC–bioautographic assay (Rakshith et al. 2013).

The endophyte *Xylaria* sp. PSU-G12, isolated from a branch of *Garcinia hombroniana* gathered in Thailand, produces two new compounds: the mellein derivative xylarellein (**9**), and the indanone derivative xylariaindanone (**10**). Furthermore, seven known compounds were also isolated: (3*R*)-5-methylmellein (**3**), (3*R*)-5-carboxylmellein (**4**), 3-hydroxy-4-methyl-1-indanone (**11**), (3*R*)-5-carbomethoxymellein (**12**), cytochalasin D (**13**), griseofulvin (**95**), and dechlorogriseofulvin (**96**). The broth extract presented antioxidant activity on the DPPH assay, thus, compounds **3**, **4**, **12**, **13**, **95**, and **96** were tested for antioxidant activity, however none of them were active (Rukachaisirikul et al. 2013). On the other hand, Pongcharoen et al. (2007) isolated the fungus *Xylaria* sp. BCC 9653 from an unidentified tree from Thailand, it yields 5-carboxylmellein (**4**) and cytochalasin D (**13**). Compounds **4** and **13** possess antimycobacterial activity against *Mycobacterium tuberculosis*, the MIC values were 394.3 and 900.7 μM, respectively.

Xylaria sp. NC1214, an endophyte isolated from *Hypnum* sp. collected in the United States (North Carolina), produces 1β,4β,7α-trihydroxyeudesmane (**14**) among other compounds (Wei et al. 2015). The eudesmane terpene **14** inhibited the growth of *Shigella sonnei*, *M. tuberculosis* and an α-hemolytic *Streptococcus* with a minimal inhibitory amount (MIA) of 300, 250, and 350 μg/disk, respectively (Wang et al. 2007). This endophyte also yields the cytotoxic cytochalasin Q (**15**) (Wei et al. 2015), which is active against *P. falciparum* K1 with an IC_{50} value of 17 μg/mL (Chinworrungsee et al. 2001).

Halorosellinic acid **(16)**, from the endophytic *Xylaria* sp. YC-10 isolated from the stem of *Azadirachta indica* from China (Wu et al. 2011), showed antimycobacterial activity against *M. tuberculosis* with MIC of 200 μg/mL and antimalarial activity against *P. falciparum* K1 with an IC_{50} value of 13 μg/mL (Chinworrungsee et al. 2001).

Tyrosol (**17**), isolated from the endophytic *Xylaria papulis* gathered from *Lepidagathis stenophylla* C.

B. Clarke ex Hayata in Taiwan (Chen et al. 2016), showed antifungal activity against the dimorphic fungi *Coccidioides posadasii,* in filamentous phase, and *Histoplasma capsulatum*, in both filamentous and yeast phases. The MIC and minimum fungicidal concentration range values were 250–4000, 30–2000, and 10–1000 μg/mL, respectively. Tyrosol (**17**) also decreased the ergosterol content and provoked leakage of nucleic acids by affecting the cell membrane permeability (Brilhante et al. 2016).

Piliformic acid (**18**) is produced by the endophyte *Xylaria cubensis* BCRC 09F 0035, isolated from the leaves of the Taiwan plant *Litsea akoensis* Hayata (Fan et al. 2014), and also from the marine fungus *Xylaria* sp. PSU-F100 (Rukachaisirikul et al. 2009). Piliformic acid (**18**) showed antimicrobial activity against *S. aureus* ATCC 25923 and MRSA with a MIC value of 200 μg/mL for both (Rukachaisirikul et al. 2009).

Cytotoxic agents

Xylaria sp. NC1214, from North Carolina, also yields four new oxygenated guaiane-type sesquiterpenes, xylaguaianols A–D (**19**–**22**), the new sesquiterpene isocadinanol A (**23**), a new α-pyrone, 9-hydroxyxylarone (**24**), the known sesquiterpenes: epi-guaidiol A (**25**), gliocladic acid (**26**), bullatantriol (**33**), hydroheptelidic acid (**67**), and four known cytochalasins, C (**27**), D (**13**), Q (**15**), and R (**28**). Cytochalasins C (**27**), D (**13**), and Q (**15**) were cytotoxic against tumour cell lines PC-3 M, NCI-H460, SF-268, MCF-7, and MDA-MB-231. Cytochalasin D (**13**) presented the highest cytotoxicity against the five cell lines with an IC_{50} range of 0.22-1.44 μM, and selectivity for line NCI-H460 with an IC_{50} value of 0.22 μM. Cytotoxicity of cytochalasins C (**27**) and Q (**15**) against cell lines PC-3 M, NCI-H460, SF-268, and MDA-MB-231 was moderate, IC_{50} values range from 0.96 to 1.72 μM for **27** and from 1.31 to 1.53 μM for **15**; for line MCF-7, both IC_{50} values were higher than 5 μM (Wei et al. 2015). Furthermore, Pongcharoen et al. (2007) established that cytochalasin D (**13**) isolated from the fungus *Xylaria* sp. BCC 9653, was cytotoxic towards African green monkey kidney fibroblast (Vero) cells with an IC_{50} value of 0.19 μM. Cytochalasin Q (**15**) is also cytotoxic against KB and BC-1 cell lines, with IC_{50} values of 3 and 1 μg/mL (Chinworrungsee et al. 2001).

Gliocladic acid (**26**), which has already been isolated from three fungal strains *Chaetomium globosum* SANK 13379, *Gliocladium virens* SANK 12679, and *Trichoderma viride* SANK 13479, is an antitumor agent on Sarcoma-37 cell line. Mice treated with a dose of 3 mg/kg/day showed 46% reduction of tumour growth and suppressed the tumour completely at 200 mg/kg (Itoh et al. 1982).

The new cytochalasin H (**29**) and cytochalasin H2 (**30**) were isolated from cultures of *Xylaria* sp. A23, an endophyte of Chinese *Annona squamosa*. Cytochalasin H2 (**30**) was cytotoxic against HeLa and 293T cell lines, at a concentration of 1 μg/mL, with inhibition of 32.8 and 25.0%, respectively (Li et al. 2012). Cytochalasin H (**29**) was cytotoxic towards human leukemia K562 cell line, with an IC_{50} value of 10.1 μM (Xu et al. 2009), and had anti-angiogenic activity on human umbilical vein endothelial cells (HUVEC), it suppressed HUVEC proliferation at concentrations ≥125 nM. It also showed in vivo anti-angiogenic effects in mice at concentrations ≥250 nM, and at concentrations ≥1000 nM angiogenesis was completely inhibited (Lee et al. 2014).

Cytochalasin B (**31**) was obtained from *X. psidii* KT30 (Tarman et al. 2011). It is a microfilament-disrupting agent that modifies many aspects of cell physiology. It showed antitumor activity in vivo against Lewis lung carcinoma, LA4 adenocarcinoma, M109 lung carcinoma, B16F10 melanoma, and P388/S and P388/ADR leukemia. It also reduces metastatic progression in mice. Additionally, **31** was safely administered by multiple routes using murine models (Trendowski et al. 2015).

It is also important to emphasize that cytochalasin inhibited actin polymerization in vitro and induced depolymerization of actin filaments in vitro (Casella et al. 1981).

5-carboxylmellein (**4**) also showed cytotoxic activity against KB and BC-1 cell lines with and an IC_{50} value of 3 μg/mL for both cell lines (Chinworrungsee et al. 2001).

Ergosterol peroxide (**5**), isolated from the endophytic *Xylaria* sp. SNB-GTC2501, also showed significant cytotoxic effects towards MRC5 cells with an IC_{50} of 1.9 μM (Sorres et al. 2015). It should be noted that Wang et al. in 2008 reported that compound **5** is cytotoxic against P388, HL-60, A549, and BEL-7402 tumor cell lines with IC_{50} values of 6.7, 15.3, 86.0, and 61.0 μM, respectively (Wang et al. 2008).

Cerevisterol (**32**) is a common compound produced by fungi, and is cytotoxic against P388 leukemia cell line with an IC_{50} of 0.12 μM (Li et al. 2007). This compound has been isolated from *Xylaria* sp. YC-10, endophyte of *A. indica* (Wu et al. 2011).

Antioxidant agents

Cerevisterol (**32**) is also an antioxidant compound with free radical-scavenging activity (SC_{50}) of 5.75 μg/mL (Cateni et al. 2015).

Tyrosol (**17**) is the major biophenol constituent on olive oil and showed antioxidant activity when added to Caco-2 human cell line (colon adenocarcinoma) with oxidized low density lipoproteins (LDL). A concentration of 0.5 mmol/L

of tyrosol (**17**) hindered the changes that oxidized LDL induce in Caco-2 cells (Giovannini et al. 1999). This compound was also identified from endophytic fungus *X. papulis* (Chen et al. 2016).

Post-menopausal osteoporosis agents

Bullatantriol (**33**) was obtained from *Xylaria* sp. NC1214 (Wei et al. 2015) and also from the plant *Homalomena occulta* (Hu et al. 2008). It stimulated differentiation of osteoblasts with significant effects of 27.2, 24.6, and 28.7, measured as alkaline phosphatase (ALP) activity in U/10 L, at concentrations of 5.16×10^{-5}, 5.16×10^{-6}, and 5.16×10^{-7} mol/L, respectively (Hu et al. 2008).

Anti-inflammatory agents

The chemical study of the organic extract of *X. cubensis* BCRC 09F 0035, isolated from the leaves of the Taiwanese plant *Litsea akoensis* Hayata, led to the isolation of six new metabolites and seven known compounds. The new compounds are: the sesquiterpenoids 10-hydroxythujopsene (**34**), akotriol (**35**), and xylaritriol (**36**), the diterpenoid cubentriol (**37**), the aliphatic derivative akoenic acid (**38**), the alkaloid akodionine (**39**); additionally, the following known compounds were isolated: the isocoumarin akolitserin or xylarellein (**9**), (–)-(*R*)-5-(methoxycarbonyl) mellein or 5-carbomethoxymellein (**12**), (–)-7-(*R*)-hydroxymellein (**40**), (*R*)-5-methylmellein (**3**), (*R*)-8-methoxymellein (**41**), (*S*)-8-methoxymellein (**42**), (+)-(*S*)-piliformic acid (**18**), methyl 1*H*-indole-3-carboxylate (**43**), and 4-(2-hydroxyethyl)phenol (**44**). Compounds **12**, **18** and **38** were tested for anti-inflamatory activity in lipopolysaccharide-activated RAW 264.7 murine macrophages. Only (–)-(*R*)-7-hydroxymellein (**40**) inhibited the proinflammatory cytokine interleukin-6 (IL-6) with an IC_{50} value of 9.4 μM (Fan et al. 2014).

X. papulis produces two new isopimarane-type diterpene glycosides compounds, xylapapusides A (**45**) and B (**46**), and five known compounds, elaeicolaside B (**47**), tyrosol (**17**), *N*-acetyltyramine (**48**), hypoxylonol A (**49**), and xylaranol B (**75**). Compounds **45**-**47** and **48** were tested for anti-inflammatory activity in lipopolysaccharide-activated RAW 264.7 murine macrophages. Nitric oxide (NO) production and cell viability were measured at a concentration of 100 μM. Compounds **45**–**47** were the most active, showing NO production induced values of 65.7, 88.7 and 78.3%, compound **48** induced 105.2% of NO production. Cell viability was not affected (Chen et al. 2016).

Hypoglycemic agents

The endophyte *Xylaria feejensis* was isolated from *Hintonia latiflora* a plant from Mexico, widely used as an antidiabetic herbal drug in Mexico and Europe. The following compounds were isolated from its extract: pestalotin 4′-*O*-methyl-*β*-mannopyranoside (**50**) and 3*S*,4*R*-(+)-4-hydroxymellein (**51**), two new natural product; and five known compounds, 3*S*,4*S*-(+)-4-hydroxymellein (**52**), 3*S*-(+)-8-methoxymellein (**42**), (4*S*,5*S*,6*S*)-4-hydroxy-3-methoxy-5-methyl-5,6-epoxycyclohex-2-enone or coriloxine (**68**), 2-hydroxy-5-methoxy-3-methylcyclohexa-2,5-diene-1,4-dione (**69**), and 4*R*,5*R*-dihydroxy-3-methoxy-5-methylcyclohexen-2-en-1-one (**53**). The isocumarins **51** and **52** inhibited *S. cerevisiae* α-glucosidase (αGHY), with IC_{50} values of 441 and 549 μM, respectively, and their activity was comparable to that of acarbose (IC_{50} of 545 μM). Compounds **51** and **52** can be considered for type II diabetes mellitus treatment. In addition, molecular docking predicted that they bind to αGHY in a site different from the catalytic domain thus suggesting an allosteric type of inhibition (Rivera-Chávez et al. 2015).

Agricultural potential

Insecticidal agents

The endophyte *Xylaria* sp. XC-16 from *Toona sinensis*, a plant that grows in China, produces two new cytochalasans, cytochalasin Z27 (**54**) and cytochalasin Z28 (**93**), together with three known metabolites, seco-cytochalasin E (**55**), cytochalasin Z18 (**56**), and cytochalasin E (**57**). Cytochalasin E (**57**) was the most active compound. It was toxic against brine shrimp with a LC_{50} of 2.79 μM, which is comparable to the commercial insecticidal toosendanin ($LC_{50} = 4.03$ μM). Compounds **54**-**55** and **93** showed low toxicity toward brine shrimp, ≤10% mortality at 50 μM (Zhang et al. 2014).

Xylaria sp., isolated from *Vitis labrusca* collected in Canada, produces two new compounds, 13-*O*-methyl-(5*R*) diplosporin (**58**) and agistatine D (**59**), and the known compounds coriloxine (**68**), 3-methoxymethyl derivative of agistatine D (**60**), (5*R*)-diplosporin (**61**), 5-carboxylmellein (**4**) and 5-methoxycarbonylmellein (**12**). Compounds **59**-**61** did not show antibacterial or antifungal activity against *B. subtilis*, *Pseudomonas fluorescens* and *S. cerevisiae* (Ibrahim et al. 2014). However, in a previous study, diplosporin (**58**) was toxic to *Spodoptera frugiperda.* It suppresses the growth rate of *S. frugiperda* to 50% when added at 1000 μg/mL to artificial diet (Wicklow et al. 2011).

The chemical study of organic extract from endophytic *Xylaria* sp. YC-10 isolated from *A. indica* led to the identification of eleven known metabolites: 5-hydroxymellein (**62**), 5-methylmellein (**3**), 5-carboxylmellein (**4**), hymatoxin C (**63**), hymatoxin D (**64**), halorosellinic acid (**16**), cerebroside C (**65**), (2*S*,3*S*,4*R*,2′*R*)-2-(2′-hydroxytetra-cosanoylamino)octadecane-1,3,4-triol (**66**), cerevisterol (**32**). All the compounds showed weak insecticidal activity against third instar larvae of *Plutella xylostella* at concentrations of 5 mg/mL, using the conventional leaf disk method (Wu et al. 2011). Even though their insecticide activity is low, they can be considered as prototypes for preparing semisynthetic derivatives in order to improve their insecticidal potential.

Hydroheptelidic acid (**67**) isolated from *Xylaria* sp. NC1214 (Wei et al. 2015), were previously identified in the fungal endophyte of balsam fir *Abies balsamea* L., *Phyllosticta* sp. strain 76. This compound was toxic to the spruce budworm *Choristoneura fumiferana* Clem. (12% of survival) when 16.8 µmol of compound was added to artificial diet (Calhoun et al. 1992).

Phytotoxic agents

The strain SM3e-1b, identified as *X. feejensis*, produces phytotoxic compounds against seedlings of *Trifolium pratense*, *Medicago sativa*, *Panicum miliaceum*, and *Amaranthus hypochondriacus*. *X. feejensis* SM3e-1b was obtained from leaves of Mexican *Sapium macrocarpum* and the chemical study of its organic extract led to the isolation of three known metabolites: coriloxine (**68**), 2-hydroxy-5-methoxy-3-methylcyclohexa-2,5-diene-1,4-dione (**69**), and 2,6-dihydroxy-5-methoxy-3-methylcyclohexa-2,5-diene-1,4-dione or fumiquinone B (**70**). In addition, four semisynthetic compounds from coriloxine (**68**) were prepared: (4*R*,5*S*,6*R*)-6-chloro-4,5-dihydroxy-3-methoxy-5-methylcyclohex-2-enone (**68a**), 6-hydroxy-5-methyl-3-(methylamino)cyclohexa-2,5-diene-1,4-dione (**68b**), (4*R*,5*R*,6*R*)-4,5-dihydroxy-3-methoxy-5-methyl-6-(phenylamino)cyclohex-2-enone (**68c**), and 2-((4-butylphenyl)amino)-5-methoxy-3-methylcyclohexa-2,5-diene-1,4-dione (**68d**). The seven compounds showed phytotoxic effect on the four weeds and on three physiological processes: germination, root elongation and seedling respiration. The IC_{50} range was of 0.2 to >1.2 mM for germination, 0.1 to >1.2 mM for root growth, and 0.7 to >1.2 mM for seedling respiration in the four plants. Inhibition is comparable to that of herbicides glyphosate and hexazinone (García-Méndez et al. 2016).

It is known that the fungi which produce VOCs are useful for mycofumigation or biofumigation against weeds and microbial plant pathogens (Stinson et al. 2003; Macías-Rubalcava et al. 2010). In relation to genus *Xylaria*, only one endophytic isolate is reported as VOCs producer: *Xylaria* sp. PB3f3, an endophyte from Mexican *Haematoxylon brasiletto*, it yields 40 volatiles during its growth time, including alkanes, esters, sesquiterpenoids, alcohols, amines, ketones, carboxylic acids, and one ether. The major compounds are thujopsene (**71**) and 3-methyl-1-butanol (**72**), at 10 days of culture; an unidentified amine and 2-methyl-1-butanol (**73**) at day 20; and 2-methyl-1-propanol (**74**) at day 30. Volatiles are phytotoxic against *A. hypochondriacus* and *Solanum lycopersicum*, and the pure compounds 2-methyl-1-propanol and 2- methyl-1-butanol significantly suppress the germination and root growth of *A. hypochondriacus* and *S. lycopersicum* in an IC_{50} value range of 4.6-130 µg/mL (Sánchez-Ortiz et al. 2016).

Cytochalasin H (**29**), isolated from *Xylaria* sp. A23 (Li et al. 2012), acts as a plant growth regulator in tobacco. At a concentration of 10^{-2}–10^{-4} M, it inhibits the floral development of tobacco plants (Wells et al. 1976).

Cytochalasin E (**57**) isolated from the endophytic *Xylaria* sp. XC-16, also showed phytotoxic effects on *Lactuca sativa* and *Raphanus sativus* L. seedlings in a range of 10–80 µM, which is higher than that of glyphosate (Zhang et al. 2014).

Borgschulte et al. (1991) reported that hymatoxins C (**63**) and D (**64**) are phytotoxins because that cause necrosis in leaves and suppress cambium development. These compounds have been isolated from the endophyte *Xylaria* sp. YC-10 (Wu et al. 2011).

Cerebroside C (**65**), a glycosphingolipid isolated from *Xylaria* sp. YC-10 (Wu et al. 2011), induces tolerance at low temperatures on *Triticum aestivum*. Seed germination rate and root growth increased when cerebroside C (**65**) was added to media at a concentration of 20 µg/mL. Germination rate was higher (77.8%), germination time shorter (6.19 days), and root growth increased by 13.7% compared to controls (Li et al. 2013).

Xylaranol B (**75**), isolated from the endophytic fungus *X. papulis* (Chen et al. 2016), showed phytotoxic activity on radish seeds (*Raphanus sativus*) at a concentration of 100 mg/mL, inhibiting approximately 60% of seed germination, which is comparable to the inhibition caused by glyphosate (75%) (Amand et al. 2012).

Antifungal agents

The new guaiane sesquiterpenes (1*S*,2*S*,4*S*,5*S*,7*R*,10*R*)-guaiane-2,10,11,12-tetraol (**76**), (1*S*,2*S*,4*R*,5*R*,7*R*,10*R*)-guaiane-2,4,10,11,12-pentaol (**77**), (1*S*,4*R*,5*S*,7*R*,10*R*)-guaiane-4,5,10,11,12-pentaol (**78**), (1*R*,4*S*,5*R*,7*R*,10*R*)-guaiane-1,5,10,11,12-pentaol (**79**), and (1*R*,4*R*,5*R*,7*R*,10*R*)-11-methoxyguaiane-4,10,12-triol (**80**) were isolated from *Xylaria* sp.YM311647 of chinese *A. indica*. All the compounds were antifungal against *Pyricularia oryzae* and

Hormodendrum compactum, showing MIC values from 32 to 256 μg/mL. Compounds **78–80** inhibited the growth of *C. albicans* with MIC values of 64 μg/mL for compound **78** and, 32 μg/mL, for compounds **79** and **80**. In addition, compound **78** inhibited *A. niger* and *H. compactum*, MIC value of 64 μg/mL (Huang et al. 2015). This isolate also yields nine oxygenated guaiane-type sesquiterpenes: (1*S*,4*S*,5*R*,7*R*,10*R*,11*R*)-guaiane-5,10,11,12-tetraol (**81**), (1*S*,4*S*,5*S*,7*R*,10*R*,11*S*)-guaiane-1,10,11,12-tetraol (**82**), (1*S*,4*S*,5*R*,7*R*,10*R*,11*S*)-guaiane-5,10,11,12-tetraol (**83**), (1*S*,4*S*,5*S*,7*R*,10*R*,11*R*)-guaiane-1,10,11,12-tetraol (**84**), (1*R*,3*S*,4*R*,5*S*,7*R*,10*R*,11*S*)-guaiane-3,10,11,12-tetraol (**85**), (1*R*,3*R*,4*R*,5*S*,7*R*,10*R*,11*R*)-guaiane-3,10,11,12-tetraol (**86**), (1*R*,4*S*,5*S*,7*S*,9*R*,10*S*,11*R*)-guaiane-9,10,11,12-tetraol (**87**), (1*R*,4*S*,5*S*,7*R*,10*R*,11*S*)-guaiane-10,11,12-triol (**88**), (1*R*,4*S*,5*S*,7*R*,10*R*,11*R*)-guaiane-10,11,12-triol (**89**); and three isopimarane diterpenes: 14a,16-epoxy-18-norisopimar-7-en-4a-ol (**90**), 16-*O*-sulfo-18-norisopimar-7-en-4a,16-diol (**91**), 9-deoxy-hymatoxin A (**92**). The sesquiterpenes were active against *C. albicans* and *H. compactum* with MIC values ranging from 32 to 256 μg/mL, they also showed moderate or weak antifungal activities against *A. niger*, *P. oryzae*, and *H. compactum*. Furthermore, the diterpenes were more active, compound **92** had a MIC value of 16 μg/mL against *C. albicans* and *P. oryzae*, and of 32 μg/mL against *A. niger* (Wu et al. 2014).

Cytochalasin Z28 (**93**) isolated from the endophyte *Xylaria* sp. XC-16, displayed antifungal activity against the plant pathogen *Gibberella saubinetti* (MIC of 12.5 μM), it was more active than the fungicide hymexazol with a MIC value of 25 μM (Zhang et al. 2014).

The nonenolide named xyolide (**94**), (4*S*,7*S*,8*S*,9*R*)-4-*O*-succinyl-7,8-dihydroxy-9-heptyl-nonen-9-olide, was isolated from the Amazonian endophytic fungus *X. feejeensis* from *Croton lechleri*. Compound **94** is active against the plant pathogenic oomycete *Pythium ultimum* with a MIC value of 425 μM (Baraban et al. 2013).

Interestingly, various isolates of *Xylaria* produce griseofulvin (**95**); *Xylaria* sp. strain F0010 isolated from *Abies holophylla* (Park et al. 2005), *Xylaria* sp. PSU-G12 from *G. hombroniana* (Rukachaisirikul et al. 2013), *X. cubensis* from *Asimina triloba* (Sica et al. 2016), 13 strains of *Xylaria* sp. Isolated from *Pinus strobus*, and six strains from *Vaccinium angustifolium* (Richardson et al. 2014). Some of these strains also produce dechlorogriseofulvin (**96**) (Park et al. 2005; Rukachaisirikul et al. 2013; Richardson et al. 2014). Griseofulvin (**95**) inhibits the growth of fungal plant pathogens, but not of oomycetes (Richardson et al. 2014). It inhibits *Alternaria mali, Botrytis cinerea, Colletotrichum gloeosporioides*, *Corticium sasaki, Fusarium oxysporum* and *Magnaporthe grisea* in in vitro experiments, with IC_{50} values of 18.0, 5.0, 1.7, 11.0, 30.0, and 1.7 μg/mL, respectively. Dechlorogriseofulvin (**96**) showed weak antifungal activity, with an IC_{50} value >200 μg/mL for each fungi. It has also been demonstrated that griseofulvin (**95**) inhibits *M. grisea, C. sasaki, B. cinerea*, *Puccinia recondite*, and *Blumeria graminis* f. sp. *hordei* in in vivo experiments, with a percentage of fungal control of 95, 100, 60, 90 and 90, respectively, at 150 μg/mL. Furthermore, dechlorogriseofulvin (**96**) at 150 μg/mL has 70, 25 and 93% of fungal control for *C. sasaki, B. cinerea* and *B. graminis* f. sp. *hordei* in vivo (Park et al. 2005). Nowadays, griseofulvin (**95**) is used for the treatment of skin diseases caused by fungi such as *Trichophyton* species (Richardson et al. 2014). These strains may be useful to obtain griseofulvin by biotechnological processes.

Table 1 shows the structures of the secondary metabolites recently isolated from endophytic *Xylaria* species, and the source and biological activity of each compound. Furthermore, it includes the isolated secondary metabolites that did not show any significant activity in preliminary studies but are nonetheless candidates to further study their biological activity. Finally, four bioactive semisynthetic derivatives are shown.

Conclusion

At present, the endophytic fungi research including *Xylaria* species is basically focused in isolation and identification, and on exploring the biological activity of secondary metabolites produced. However, it is also necessary to deepen the biological, chemical and biotechnological studies of these microorganisms to optimize their use as a potential source of new drugs and agrochemicals, or for development of biocontrol agents. Furthermore, it is well known that production of secondary metabolites is a process highly influenced by several physicochemical factors particularly temperature, pH and oxygenation, and the presence or absence of certain nutrients. Therefore, it is of paramount importance to optimize the culture conditions in order to improve the development of new pharmacological compounds and agrochemical products.

To promote the finding of endophytic *Xylaria* species, which would potentially produce new bioactive secondary metabolites, there are two main strategies: first, the selection of endophytes that possess an antagonic effect on other microorganisms, including endophytic fungi, human pathogenic fungi, or phytopathogenic fungi with agricultural importance; and second, a dereplication strategy.

The endophytic *Xylaria* species have been found associated to both vascular and nonvascular plants and, as has been shown in this review, the structural diversity of the bioactive secondary metabolites from endophytic *Xylaria* species opens the opportunity to finding new compounds, and even new chemical skeletons, that can be used by

Table 1 Recently reported bioactive secondary metabolites from endophytic *Xylaria* species

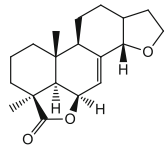
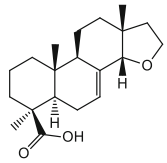
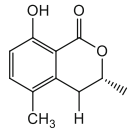
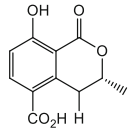
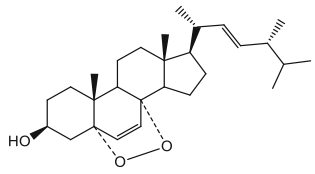
Secondary metabolite	Structure	Endophyte/name of strain	Host plant	Potential features (bioactivity)
Xylabisboein A (**1**)		*Xylaria* sp. SNB-GTC2501	*Bisboecklera microcephala* (Sorres et al. 2015)	Antimicrobial activity against *S. aureus*, *T. rubrum* and *C. albicans*
Xylabisboein B (**2**)				
5-Methylmellein (**3**)		*Xylaria* sp. SNB-GTC2501	*Bisboecklera microcephala* (Sorres et al. 2015)	Antimicrobial activity against *S. aureus*, *T. rubrum* and *C. albicans*
		Xylaria sp. PSU-G12	*Garcinia hombroniana* (Rukachaisiri-kul et al. 2013)	Insecticidal activity against *P. xylostella*
		Xylaria cubensis BCRC 09F 0035	*Litsea akoensis* (Fan et al. 2014)	
		Xylaria sp. YC-10	*Azadirachta indica* (Wu et al. 2011)	
Mellein-5-carboxylic acid or 5-Carboxylmellein (**4**)		*Xylaria* sp. SNB-GTC2501	*Bisboecklera microcephala* (Sorres et al. 2015)	Antimicrobial activity against *S. aureus*, *T. rubrum, C. albicans* and *M. tuberculosis*
		Xylaria sp. PSU-G12	*Garcinia hombroniana* (Rukachaisiri-kul et al. 2013)	Antimalarial activity against *P. falciparum* K1
		Xylaria sp. BCC 9653	Unidentified tree (Pongcharoen et al. 2007)	Cytotoxic activity against KB and BC-1 cell lines
		Xylaria sp.	*Vitis labrusca* (Wicklow et al. 2011)	Insecticidal activity against *P. xylostella*
		Xylaria sp. YC-10	*Azadirachta indica* (Wu et al. 2011)	
Ergosterol peroxide (**5**)		*Xylaria* sp. SNB-GTC2501	*Bisboecklera microcephala* (Sorres et al. 2015)	Antimicrobial activity against *S. aureus*, *T. rubrum* and *C. albicans*
				Cytotoxic activity against MRC5, P388, HL-60, A549 and BEL-7402 cell lines

Table 1 continued

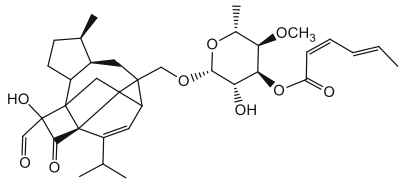
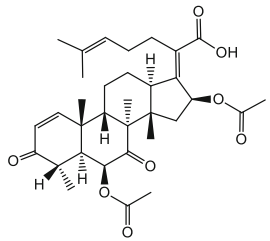
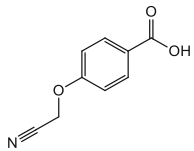
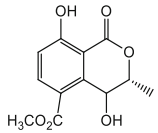
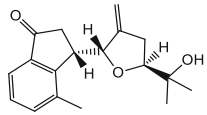
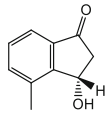
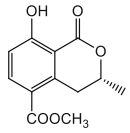
Secondary metabolite	Structure	Endophyte/name of strain	Host plant	Potential features (bioactivity)
Zofimarin (**6**)		*Xylaria* sp. Acra L38	*Aquilaria crassna* (Chaichanan et al. 2014)	Antifungal activity against *C. albicans*, *S. cerevisiae*, *C. neoformans*, and *Aspergillus* sp.
Helvolic acid (**7**)		*Xylaria* sp.	*Anoectochilus setaceus* (Ratnaweera et al. 2014)	Antibacterial activity against *B. subtilis* and anti-MRSA
4-Cyanomethoxy benzoic acid (**8**)		*Xylaria* sp. strain FPLX-10 *Xylaria psidii* KT30	*Ficus pumila* Linn. (Rakshith et al. 2013) *Kappaphycus alvarezii* (Tarman et al. 2011)	Antimicrobial activity against *E. coli*, *V. parahaemolyticus*, *S. aureus, L. monocytogenes, C. albicans* and *A. niger*
Xylarellein (**9**)[a]		*Xylaria* sp. PSU-G12 *Xylaria cubensis* BCRC 09F 0035	*Garcinia hombroniana* (Rukachaisiri-kul et al. 2013) *Litsea akoensis* (Fan et al. 2014)	No activity is reported
Xylariaindanone (**10**)[a]		*Xylaria* sp. PSU-G12	*Garcinia hombroniana* (Rukachaisiri-kul et al. 2013)	No activity is reported
3-Hydroxy-4-methyl-1-indanone (**11**)[b]		*Xylaria* sp. PSU-G12	*Garcinia hombroniana* (Rukachaisiri-kul et al. 2013)	No activity is reported
5-Carbomethoxymellein (**12**)[b]		*Xylaria* sp. PSU-G12 *Xylaria cubensis* BCRC 09F 0035 *Xylaria* sp.	*Garcinia hombroniana* (Rukachaisiri-kul et al. 2013) *Litsea akoensis* (Fan et al. 2014) *Vitis labrusca* (Wicklow et al. 2011)	No activity is reported

Table 1 continued

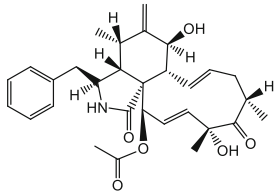
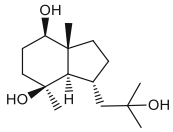
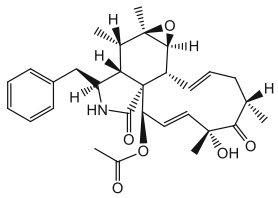
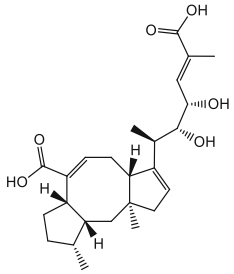
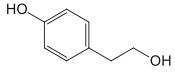
Secondary metabolite	Structure	Endophyte/name of strain	Host plant	Potential features (bioactivity)
Cytochalasin D (**13**)		*Xylaria* sp. PSU-G12	*Garcinia hombroniana* (Rukachaisiri-kul et al. 2013)	Antimycobacterial activity against *M. tuberculosis*
		Xylaria sp. BCC 9653	Unidentified tree (Pongcharoen et al. 2007)	Cytotoxic activity against tumour cell lines Vero, PC-3 M, NCI-H460, SF-268, MCF-7 and MDA-MB-231
		Xylaria sp. NC1214	*Hypnum* sp. (Wei et al. 2015)	
1β,4β,7α-Trihydroxyeudesmane (**14**)		*Xylaria* sp. NC1214	*Hypnum* sp. (Wei et al. 2015)	Antibacterial activity against *S. sonnei*, *M. tuberculosis* and α-hemolytic *Streptococcus*
Cytochalasin Q (**15**)		*Xylaria* sp. NC1214	*Hypnum* sp. (Wei et al. 2015)	Antimalarial activity against *P. falciparum* K1 Cytotoxic activity against tumour cell lines KB, BC-1, PC-3 M, NCI-H460, SF-268, MCF-7, and MDA-MB-231
Halorosellinic acid (**16**)		*Xylaria* sp. YC-10	*Azadirachta indica* (Wu et al. 2011)	Antimycobacterial activity against *M. tuberculosis* Antimalarial activity against *P. falciparum* K1 Insecticidal activity against *P. xylostella*
Tyrosol (**17**)		*Xylaria papulis*	*Lepidagathis stenophylla* (Chen et al. 2016)	Antifungal activity against *C. posadasii,* in filamentous phase, and *H. capsulatum* Antioxidant activity in Caco-2 cell line

Table 1 continued

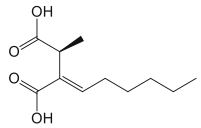
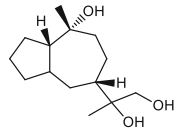
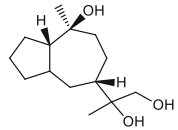
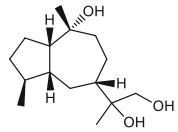
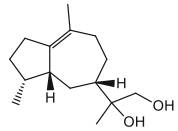
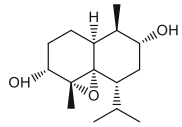
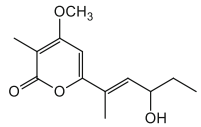
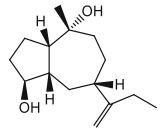
Secondary metabolite	Structure	Endophyte/name of strain	Host plant	Potential features (bioactivity)
Piliformic acid (**18**)		*Xylaria cubensis* BCRC 09F 0035	*Litsea akoensis* (Fan et al. 2014)	Antimicrobial activity against *S. aureus* ATCC 25923 and MRSA
Xylaguaianol A (**19**)[a]		*Xylaria* sp. NC1214	*Hypnum* sp. (Wei et al. 2015)	No activity is reported
Xylaguaianol B (**20**)[a]				
Xylaguaianol C (**21**)[a]				
Xylaguaianol D (**22**)[a]				
Isocadinanol A (**23**)[a]				
9-Hydroxyxylarone (**24**)[a]				
Epi-guaidiol A (**25**)[b]				

Table 1 continued

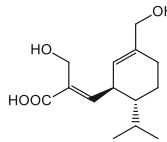
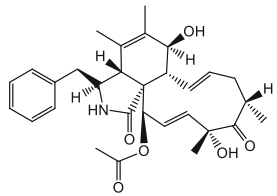
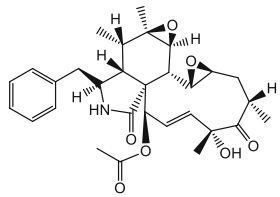
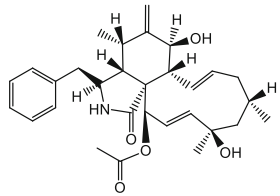
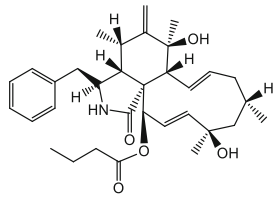
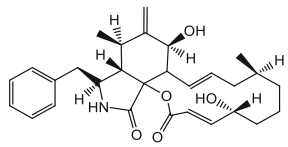
Secondary metabolite	Structure	Endophyte/name of strain	Host plant	Potential features (bioactivity)
Gliocladic acid (**26**)		*Xylaria* sp. NC1214	*Hypnum* sp. (Wei et al. 2015)	Antitumor agent on Sarcoma-37 cell line
Cytochalasin C (**27**)		*Xylaria* sp. NC1214	*Hypnum* sp. (Wei et al. 2015)	Cytotoxic activity against tumour cell lines PC-3M, NCI-H460, SF-268, MCF-7, and MDA-MB-231
Cytochalasin R (**28**)[b]		*Xylaria* sp. NC1214	*Hypnum* sp. (Wei et al. 2015)	No activity is reported
Cytochalasin H (**29**)		*Xylaria* sp. A23	*Annona squamosa* (Li et al. 2012)	Cytotoxic activity against K562 cell line Anti-angiogenic activity HUVEC cells Phytotoxic activity against tobacco plants
Cytochalasin H2 (**30**)		*Xylaria* sp. A23	*Annona squamosa* (Li et al. 2012)	Cytotoxic activity against HeLa and 293T cell lines
Cytochalasin B (**31**)		*Xylaria psidii* KT30	*Kappaphycus alvarezii* (Tarman et al. 2011)	Antitumor activity against Lewis lung carcinoma, LA4, M109, B16F10, P388/S and P388/ADR leukemia cell lines

Table 1 continued

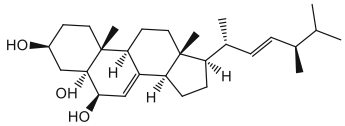
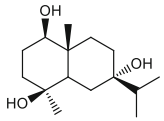
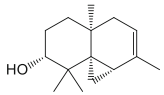
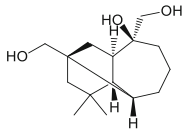
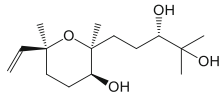
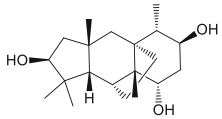
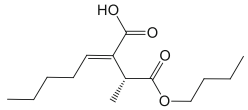
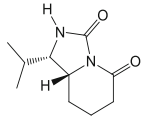
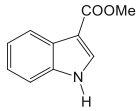
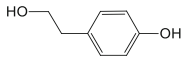
Secondary metabolite	Structure	Endophyte/name of strain	Host plant	Potential features (bioactivity)
Cerevisterol (**32**)		*Xylaria* sp. YC-10	*Azadirachta indica* (Wu et al. 2011)	Cytotoxic activity against P388 cell line Antioxidant activity Insecticidal activity against *P. xylostella*
Bullatantriol (**33**)		*Xylaria* sp. NC1214	*Hypnum* sp. (Wei et al. 2015)	Post-menopausal osteoporosis agent
10-Hydroxythujopsene (**34**)[a]		*Xylaria cubensis* BCRC 09F 0035	*Litsea akoensis* (Fan et al. 2014)	No activity is reported
Akotriol (**35**)[a]				
Xylaritriol (**36**)[a]				
Cubentriol (**37**)[a]				
Akoenic acid (**38**)[a]				
Akodionine (**39**)[a]				
Methyl 1*H*-indole-3-carboxylate (**43**)[b]				
4-(2-Hydroxy-ethyl)phenol (**44**)[b]				

Table 1 continued

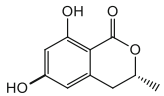
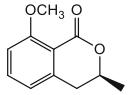
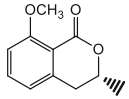
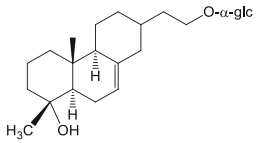
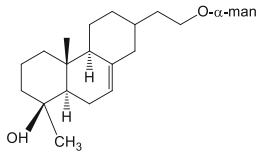
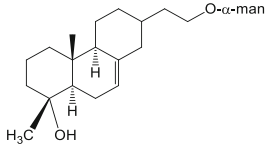
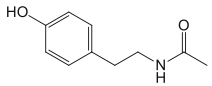
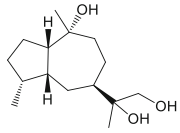
Secondary metabolite	Structure	Endophyte/name of strain	Host plant	Potential features (bioactivity)
(–)-7-(*R*)-Hydroxymellein (**40**)		*Xylaria cubensis* BCRC 09F 0035	*Litsea akoensis* (Fan et al. 2014)	Anti-inflammatory agent: inhibits IL-6 production
3*R*-8-Methoxymellein (**41**)		*Xylaria cubensis* BCRC 09F 0035	*Litsea akoensis* (Fan et al. 2014)	No activity is reported
		Xylaria feejensis	*Hintonia latiflora* (Rivera-Chávez et al. 2015)	
3*S*-8-Methoxymellein (**42**)				
Xylapapuside A (**45**)		*Xylaria papulis*	*Lepidagathis stenophylla* (Chen et al. 2016)	Anti-inflammatory agent: induce NO production
Xylapapuside B (**46**)				
Elaeicolaside B (**47**)				
N-acetyltyramine (**48**)				
Hypoxylonol A (**49**)[b]		*Xylaria papulis*	*Lepidagathis stenophylla* (Chen et al. 2016)	No activity is reported

Table 1 continued

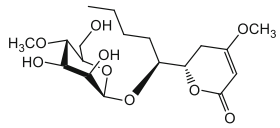
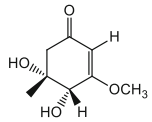
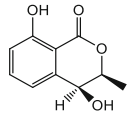
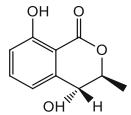
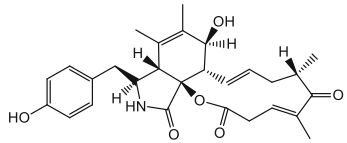
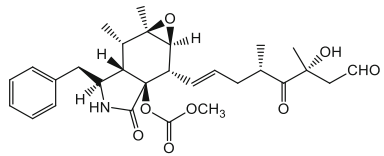
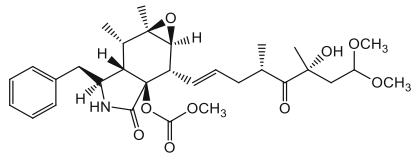
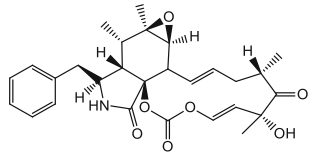
Secondary metabolite	Structure	Endophyte/name of strain	Host plant	Potential features (bioactivity)
Pestalotin 4′-*O*-methyl-*β*-mannopyranoside (**50**)[a]		*Xylaria feejensis*	*Hintonia latiflora* (Rivera-Chávez et al. 2015)	No activity is reported
4*R*,5*R*-Dihydroxy-3-methoxy-5-methylcyclohexen-2-en-1-one (**53**)[b]				
3*S*,4*R*-(+)-4-Hydroxymellein (**51**)		*Xylaria feejensis*	*Hintonia latiflora* (Rivera-Chávez et al. 2015)	Hypoglycemic agents: inhibit *S. cerevisiae* α-glucosidase
3*S*,4*S*-(+)-4-Hydroxymellein (**52**)				
Cytochalasin Z27 (**54**)		*Xylaria* sp. XC-16	*Toona sinensis* (Zhang et al. 2014)	Insecticidal activity against brine shrimp
Seco-cytochalasin E (**55**)				
Cytochalasin Z18 (**56**)[b]		*Xylaria* sp. XC-16	*Toona sinensis* (Zhang et al. 2014)	No activity is reported
Cytochalasin E (**57**)		*Xylaria* sp. XC-16	*Toona sinensis* (Zhang et al. 2014)	Insecticidal activity against brine shrimp. Phytotoxic activity on *L. sativa* and *R. sativus*

Table 1 continued

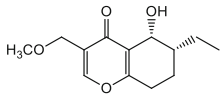
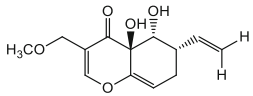
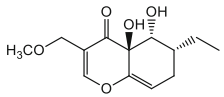
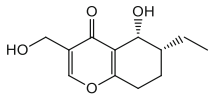
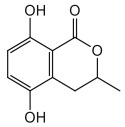
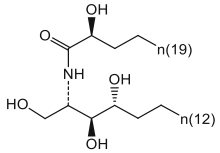
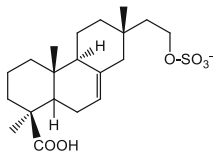
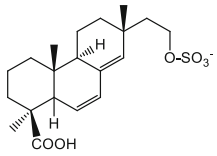
Secondary metabolite	Structure	Endophyte/name of strain	Host plant	Potential features (bioactivity)
13-*O*-Methyl-(5*R*) diplosporin (**58**)		*Xylaria* sp.	*Vitis labrusca* (Wicklow et al. 2011)	Insecticidal activity against *S. frugiperda*
Agistatine D (**59**)[a]		*Xylaria* sp.	*Vitis labrusca* (Wicklow et al. 2011)	No activity is reported
3-Methoxymethyl derivative of agistatine D (**60**)[b]				
(5*R*)-Diplosporin (**61**)[b]				
5-Hydroxymellein (**62**)		*Xylaria* sp. YC-10	*Azadirachta indica* (Wu et al. 2011)	Insecticidal activity against *P. xylostella*
(2*S*,3*S*,4*R*,2́*R*)-2-(2́-Hydroxytetracosanoylamino)octadecane-1,3,4-triol (**66**)				
Hymatoxin C (**63**)		*Xylaria* sp. YC-10	*Azadirachta indica* (Wu et al. 2011)	Insecticidal activity against *P. xylostella* Phytotoxic activity
Hymatoxin D (**64**)				

Table 1 continued

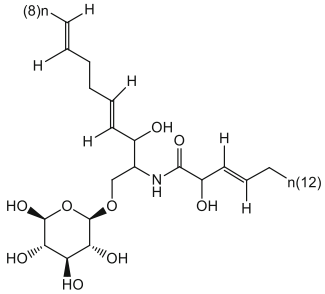
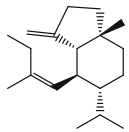
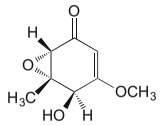
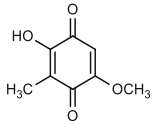
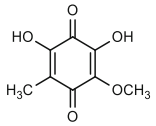
Secondary metabolite	Structure	Endophyte/name of strain	Host plant	Potential features (bioactivity)
Cerebroside C (**65**)		*Xylaria* sp. YC-10	*Azadirachta indica* (Wu et al. 2011)	Insecticidal activity against *P. xylostella.* Increases growth and induces tolerance at low temperature on *T. aestivum*
Hydroheptelidic acid (**67**)		*Xylaria* sp. NC1214	*Hypnum* sp. (Wei et al. 2015)	Insecticidal activity against spruce budworm *C. fumiferana*
Coriloxine (**68**)		*Xylaria feejensis* *Xylaria* sp. *Xylaria feejensis* SM3e-1b	*Hintonia latiflora* (Rivera-Chávez et al. 2015) *Vitis labrusca* (Wicklow et al. 2011) *Sapium macrocarpum* (García-Méndez et al. 2016)	Phytotoxic activity against *T. pratense*, *M. sativa*, *P. miliaceum*, and *A. hypochondriacus*
2-Hydroxy-5-methoxy-3-methylcyclohexa-2,5-diene-1,4-dione (**69**)		*Xylaria feejensis* SM3e-1b	*Sapium macrocarpum* (García-Méndez et al. 2016)	Phytotoxic activity against *T. pratense*, *M. sativa*, *P. miliaceum*, and *A. hypochondriacus*
Fumiquinone B (**70**)				

Table 1 continued

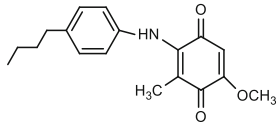
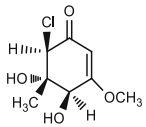
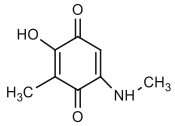
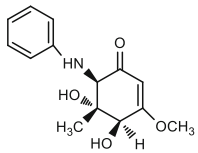
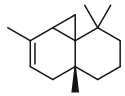
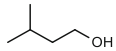
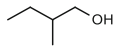
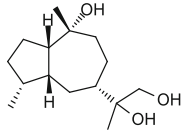
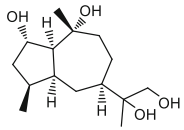
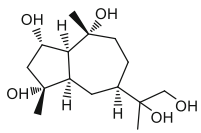
Secondary metabolite	Structure	Endophyte/name of strain	Host plant	Potential features (bioactivity)
(4*R*,5*S*,6*R*)-6-Chloro-4,5-dihydroxy-3-methoxy-5-methylcyclohex-2-enone (**68a**)[c]		*Xylaria feejensis* SM3e-1b	*Sapium macrocarpum* (García-Méndez et al. 2016)	Phytotoxic activity against *T. pratense*, *M. sativa*, *P. miliaceum*, and *A. hypochondriacus*
6-Hydroxy-5-methyl-3-(methylamino)cyclohexa-2,5-diene-1,4-dione (**68b**)[c]				
(4*R*,5*R*,6*R*)-4,5-Dihydroxy-3-methoxy-5-methyl-6-(phenylamino)cyclohex-2-enone (**68c**)[c]				
2-((4-Butylphe-nyl)amino)-5-methoxy-3-methylcyclohexa-2,5-diene-1,4-dione (**68d**)[c]				
Thujopsene (**71**)		*Xylaria* sp. PB3f3	*Haematoxylon brasiletto* (Sánchez-Ortiz et al. 2016)	Phytotoxic activity against *A. hypochondriacus* and *S. lycopersicum*
3-Methyl-1-butanol (**72**)				
2-Methyl-1-butanol (**73**)				
2-Methyl-1-propanol (**74**)				
Xylaranol B (**75**)		*Xylaria papulis*	*Lepidagathis stenophylla* (Chen et al. 2016)	Phytotoxic activity against *R. sativus*
(1*S*,2*S*,4*S*,5*S*,7*R*,10*R*)-Guaiane-2,10,11,12-tetraol (**76**)		*Xylaria* sp. YM311647	*Azadirachta indica* (Huang et al. 2015)	Antifungal activity against *P. oryzae* and *H. compactum*
(1*S*,2*S*,4*R*,5*R*,7*R*,10*R*)-Guaiane-2,4,10,11,12-pentaol (**77**)				

Table 1 continued

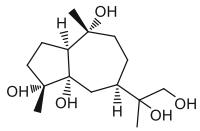
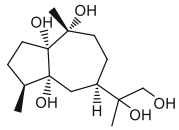
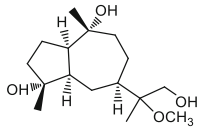
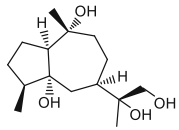
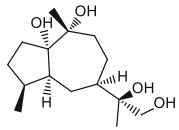
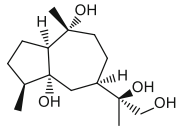
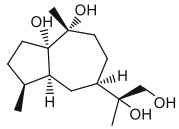
Secondary metabolite	Structure	Endophyte/name of strain	Host plant	Potential features (bioactivity)
(1*S*,4*R*,5*S*,7*R*,10*R*)-Guaiane-4,5,10,11,12-pentaol (**78**)		*Xylaria* sp. YM311647	*Azadirachta indica* (Huang et al. 2015)	Antifungal activity against *P. oryzae*, *H. compactum, C. albicans* and *A. niger*
(1*R*,4*S*,5*R*,7*R*,10*R*)-Guaiane-1,5,10,11,12-pentaol (**79**)		*Xylaria* sp. YM311647	*Azadirachta indica* (Huang et al. 2015)	Antifungal activity against *P. oryzae*, *H. compactum, C. albicans*
(1*R*,4*R*,5*R*,7*R*,10*R*)-11-Methoxyguaiane-4,10,12-triol (**80**)				
(1*S*,4*S*,5*R*,7*R*,10*R*,11*R*)-Guaiane-5,10,11,12-tetraol (**81**)		*Xylaria* sp. YM311647	*Azadirachta indica* (Huang et al. 2015)	Antifungal activity against *C. albicans*, *H. compactum*, *A. niger* and *P. oryzae*
(1*S*,4*S*,5*S*,7*R*,10*R*,11*S*)-Guaiane-1,10,11,12-tetraol (**82**)				
(1*S*,4*S*,5*R*,7*R*,10*R*,11*S*)-Guaiane-5,10,11,12-tetraol (**83**)				
(1*S*,4*S*,5*S*,7*R*,10*R*,11*R*)-Guaiane-1,10,11,12-tetraol (**84**)				

Table 1 continued

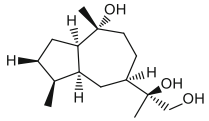
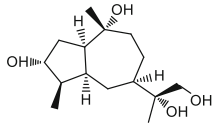
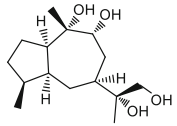
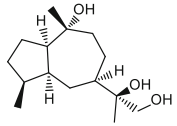
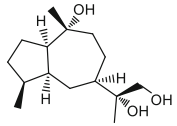
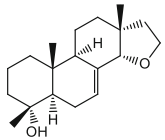
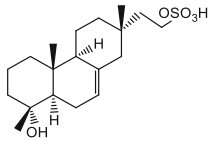
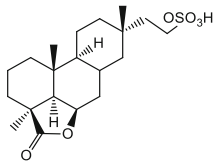
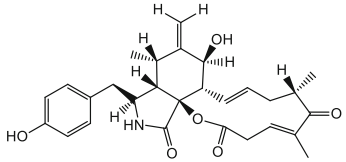
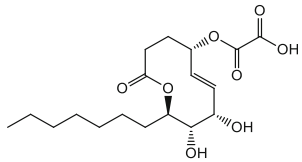
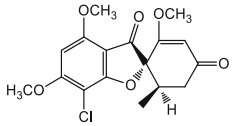
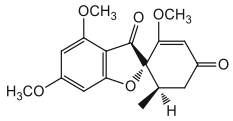
Secondary metabolite	Structure	Endophyte/name of strain	Host plant	Potential features (bioactivity)
(1*R*,3*S*,4*R*,5*S*,7*R*,10*R*,11*S*)-Guaiane-3,10,11,12-tetraol (**85**)		*Xylaria* sp. YM311647	*Azadirachta indica* (Huang et al. 2015)	Antifungal activity against *C. albicans*, *H. compactum*, *A. niger* and *P. oryzae*
(1*R*,3*R*,4*R*,5*S*,7*R*,10*R*,11*R*)-Guaiane-3,10,11,12-tetraol (**86**)				
(1*R*,4*S*,5*S*,7*S*,9*R*,10*S*,11*R*)-Guaiane-9,10,11,12-tetraol (**87**)				
(1*R*,4*S*,5*S*,7*R*,10*R*,11*S*)-Guaiane-10,11,12-triol (**88**)				
(1*R*,4*S*,5*S*,7*R*,10*R*,11*R*)-Guaiane-10,11,12-triol (**89**)				
14a,16-Epoxy-18-norisopimar-7-en-4a-ol (**90**)				
16-*O*-Sulfo-18-norisopimar-7-en-4a,16-diol (**91**)				
9-Deoxy-hymatoxin A (**92**)				

Table 1 continued

Secondary metabolite	Structure	Endophyte/name of strain	Host plant	Potential features (bioactivity)
Cytochalasin Z28 (**93**)		*Xylaria* sp. XC-16	*Toona sinensis* (Zhang et al. 2014)	Insecticidalactivity against brine shrimp. Antifungal activity against *G. saubinetti*
Xyolide (**94**)		*Xylaria feejensis*	*Croton lechleri* (Baraban et al. 2013)	Antioomycete activity against *P. ultimum*
Griseofulvin (**95**)		*Xylaria* sp. strain F0010	*Abies holophylla* (Park et al. 2005)	Antifungal activity against *A. mali, B. cinerea, C. gloeosporioides, C. sasaki, F. oxysporum, M. grisea, P. recondite*, and *B. graminis* f. sp. *hordei.* Treatment for skin diseases caused by fungi
		Xylaria sp. PSU-G12	*Garcinia hombroniana* (Rukachaisiri-kul et al. 2013)	
		Xylaria cubensis	*Asimina triloba* (Sica et al. 2016)	
		Xylaria spp.	*Pinus strobus* (Richardson et al. 2014)	
		Xylaria spp.	*Vaccinium angustifolium* (Richardson et al. 2014)	
Dechlorogriseofulvin (**96**)		*Xylaria* sp. strain F0010	*Abies holophylla* (Park et al. 2005)	Antifungal activity against *A. mali, B. cinerea, C. gloeosporioides, C. sasaki, F. oxysporum, M. grisea* and *B. graminis* f. sp. *hordei*
		Xylaria sp. PSU-G12	*Garcinia hombroniana* (Rukachaisiri-kul et al. 2013)	
		Xylaria spp.	*Vaccinium angustifolium* (Richardson et al. 2014)	

[a] New secondary metabolites and [b] known secondary metabolites produced by endophytic *Xylaria* species that did not show any significant activity in preliminary studies. Nonetheless, they are candidates to further study their biological activity. [c] Bioactive semisynthetic derivatives

themselves or as structural prototypes to develop therapeutic agents or as biopesticides. Nevertheless, the bioactive secondary metabolites produced by endophytic fungi, especially the *Xylaria* species are just beginning to be discovered.

Metabolites such as cytochalasins, guaiane sesquiterpenes, mellein derivatives and coriloxine, are common in *Xylaria* species and have important biological activity. Particularly, cytochalasins are the most important bioactive components in the genus *Xylaria*. These compounds, in addition to being cytotoxic and possessing a high chemical diversity, are a fundamental tool to understanding the importance of actin in various biological processes.

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Conflict of interst The authors declare no competing financial interest.

References

Amand S, Langenfeld A, Blond A et al (2012) Guaiane sesquiterpenes from *Biscogniauxia nummularia* featuring potent antigerminative activity. J Nat Prod 75:798–801. doi:10.1021/np2009913

Arnold AE, Lutzoni F (2007) Diversity and host range of foliar fungal endophytes: are tropical leaves biodiversity hotspots? Ecology 88:541–549. doi:10.1890/05-1459

Baraban EG, Morin JB, Phillips GM et al (2013) Xyolide, a bioactive nonenolide from an Amazonian endophytic fungus, *Xylaria feejeensis*. Tetrahedron Lett 54:4058–4060. doi:10.1016/j.tetlet.2013.05.093

Borgschulte K, Rebuffat S, Trowitzsch-Kienast W et al (1991) Isolation and structure elucidation of hymatoxins B - E and other phytotoxins from *Hypoxylon mammatum* fungal pathogen of leuce poplars. Tetrahedron 47:8351–8360. doi:10.1016/S0040-4020(01)96176-9

Brilhante RSN, Caetano ÉP, de Lima RAC et al (2016) Terpinen-4-ol, tyrosol, and β-lapachone as potential antifungals against dimorphic fungi. Braz J Microbiol. doi:10.1016/j.bjm.2016.07.015

Calhoun LA, Findlay JA, David Miller J, Whitney NJ (1992) Metabolites toxic to spruce budworm from balsam fir needle endophytes. Mycol Res 96:281–286. doi:10.1016/S0953-7562(09)80939-8

Casella JF, Flanagan MD, Lin S (1981) Cytochalasin D inhibits actin polymerization and induces depolymerization of actin filaments formed during platelet shape change. Nature 293:302–305. doi:10.1038/293302a0

Cateni F, Zacchigna M, Altieri T et al (2015) Antioxidant properties of oak bracket mushroom, *Pseudoinonotus dryadeus* (higher basidiomycetes): a mycochemical study. Int J Med Mushrooms 17:627–637. doi:10.1615/IntJMedMushrooms.v17.i7.30

Chaichanan J, Wiyakrutta S, Pongtharangkul T et al (2014) Optimization of zofimarin production by an endophytic fungus, *Xylaria* sp. Acra L38. Braz J Microbiol 45:287–293. doi:10.1590/S1517-83822014000100042

Chen Y, Chang H, Cheng M et al (2016) New chemical constituents from the endophytic fungus X*ylaria papulis* cultivated on Taiwanese *Lepidagathis stenophylla*. Rec Nat Prod 10:735–743

Chinworrungsee M, Kittakoop P, Isaka M et al (2001) Antimalarial halorosellinic acid from the marine fungus *Halorosellinia oceanica*. Bioorganic Med Chem Lett 11:1965–1969. doi:10.1016/S0960-894X(01)00327-4

Davis EC, Franklin JB, Shaw AJ, Vilgalys R (2003) Endophytic *Xylaria* (Xylariaceae) among liverworts and angiosperms: phylogenetics, distribution, and symbiosis. Am J Bot 90:1661–1667. doi:10.3732/ajb.90.11.1661

Fan N-W, Chang H-S, Cheng M-J et al (2014) Secondary metabolites from the endophytic fungus *Xylaria cubensis*. Helv Chim Acta 97:1689–1699. doi:10.1002/hlca.201400091

Gao F, Dai C, Liu X (2010) Mechanisms of fungal endophytes in plant protection against pathogens. Afr J Microbiol Res 4:1346–1351

García-Méndez MC, Macías-Ruvalcaba NA, Lappe-Oliveras P et al (2016) Phytotoxic potential of secondary metabolites and semisynthetic compounds from endophytic fungus *Xylaria feejeensis* strain SM3e-1b isolated from *Sapium macrocarpum*. J Agric Food Chem 64:4255–4263. doi:10.1021/acs.jafc.6b01111

Giovannini C, Straface E, Modesti D et al (1999) Tyrosol, the major olive oil biophenol, protects against oxidized-LDL-induced injury in Caco-2 cells. J Nutr 129:1269–1277

Guzmán-Trampe S, Rodríguez-Peña K, Espinosa-Gómez A et al (2015) Endophytes as a potential source of new antibiotics. In: Sanchez S, Demain AL (eds) Antibiotics current innovations and future trends. Caister Academic Press, Norfolk, pp 175–206

Hu YM, Liu C, Cheng KW et al (2008) Sesquiterpenoids from *Homalomena occulta* affect osteoblast proliferation, differentiation and mineralization in vitro. Phytochemistry 69:2367–2373. doi:10.1016/j.phytochem.2008.05.023

Huang R, Xie XS, Fang XW et al (2015) Five new guaiane sesquiterpenes from the endophytic fungus *Xylaria* sp. YM 311647 of *Azadirachta indica*. Chem Biodivers 12:1281–1286. doi:10.1002/cbdv.201400405

Hyde KD, Soytong K (2008) The fungal endophyte dilemma. Fungal Divers 33:163–173

Ibrahim A, Sorensen D, Jenkins HA et al (2014) New diplosporin and agistatine derivatives produced by the fungal endophyte *Xylaria* sp. isolated from *Vitis labrusca*. Phytochem Lett 9:179–183. doi:10.1016/j.phytol.2014.06.011

Itoh Y, Takahashi S, Arai M (1982) Structure of gliocladic acid. J Antibiot (Tokyo) 35:541–542

Kusari S, Hertweck C, Spiteller M (2012) Chemical ecology of endophytic fungi: origins of secondary metabolites. Chem Biol 19:792–798. doi:10.1016/j.chembiol.2012.06.004

Lee J, Yi J-M, Kim H et al (2014) Cytochalasin H, an active anti-angiogenic constituent of the ethanol extract of *Gleditsia sinensis* Thorns. Biol Pharm Bull 37:6–12. doi:10.1248/bpb.b13-00318

Li DH, Cai SX, Tian L et al (2007) Two new metabolites with cytotoxicities from deep-sea fungus, *Aspergillus sydowi* YH11-2. Arch Pharm Res 30:1051–1054

Li Y, Lu C, Huang Y et al (2012) Cytochalasin H2, a new cytochalasin, isolated from the endophytic fungus *Xylaria* sp. A23. Rec Nat Prod 6:121–126

Li HX, Xiao Y, Cao LL et al (2013) Cerebroside C increases tolerance to chilling injury and alters lipid composition in wheat roots. PLoS ONE 8:e73380. doi:10.1371/journal.pone.0073380

Macías-Rubalcava ML, Hernández-bautista BE, Oropeza F et al (2010) Allelochemical effects of volatile compounds and organic extracts from *Muscodor yucatanensis*, a tropical endophytic fungus from *Bursera simaruba*. J Chem Ecol 36:1122–1131. doi:10.1007/s10886-010-9848-5

Ogita T, Hayashi T, Satou A, Furuya K (1987) Antibiotic zofimarin. Jpn Kokai Tokkyo Koho JP S6240292 A

Park J, Choi J, Gyung GJ et al (2005) Griseofulvin from *Xylaria* sp. strain F0010, an endophytic fungus of *Abies holophylla* and its antifungal activity against plant pathogenic fungi. J Microbiol Biotechnol 15:112–117

Pongcharoen W, Rukachaisirikul V, Isaka M, Sriklung K (2007) Cytotoxic metabolites from the wood-decayed fungus *Xylaria* sp. BCC 9653. Chem Pharm Bull 55:1647–1648. doi:10.1248/cpb.55.1647

Rakshith D, Santosh P, Tarman K et al (2013) Dereplication strategy for antimicrobial metabolite using thin-layer chromatography-bioautography and LC-PDA-MS analysis. J Planar Chromatogr TLC 26:470–474. doi:10.1556/JPC.26.2013.6.2

Ratnaweera PB, Williams DE, de Silva ED et al (2014) Helvolic acid, an antibacterial nortriterpenoid from a fungal endophyte, *Xylaria* sp. of orchid *Anoectochilus setaceus* endemic to Sri Lanka. Mycology 5:23–28. doi:10.1080/21501203.2014.892905

Richardson SN, Walker AK, Nsiama TK et al (2014) Griseofulvin-producing *Xylaria* endophytes of *Pinus strobus* and *Vaccinium angustifolium*: evidence for a conifer-understory species endophyte ecology. Fungal Ecol 11:107–113. doi:10.1016/j.funeco.2014.05.004

Rivera-Chávez J, Figueroa M, González MDC et al (2015) α-Glucosidase inhibitors from a *Xylaria feejeensis* associated with *Hintonia latiflora*. J Nat Prod 78:730–735. doi:10.1021/np500897y

Rukachaisirikul V, Khamthong N, Sukpondma Y et al (2009) An [11]cytochalasin derivative from the marine-derived fungus *Xylaria* sp. PSU-F100. Chem Pharm Bull (Tokyo) 57:1409–1411. doi:10.1248/cpb.57.1409

Rukachaisirikul V, Buadam S, Sukpondma Y et al (2013) Indanone and mellein derivatives from the *Garcinia*-derived fungus *Xylaria* sp. PSU-G12. Phytochem Lett 6:135–138. doi:10.1016/j.phytol.2012.11.007

Sánchez-Ortiz BL, Sánchez-Fernández RE, Duarte G et al (2016) Antifungal, antioomycete and phytotoxic effects of volatile organic compounds from the endophytic fungus *Xylaria* sp. strain PB3f3 isolated from *Haematoxylon brasiletto*. J Appl Microbiol 120:1313–1325. doi:10.1111/jam.13101

Sica VP, Rees ER, Tchegnon E et al (2016) Spatial and temporal profiling of griseofulvin production in *Xylaria cubensis* using mass spectrometry mapping. Front Microbiol. doi:10.3389/fmicb.2016.00544

Song F, Wu S, Zhai Y et al (2014) Secondary metabolites from the genus *Xylaria* and their bioactivities. Chem Biodivers 11:673–694. doi:10.1002/cbdv.20120028

Sorres J, Nirma C, Touré S et al (2015) Two new isopimarane diterpenoids from the endophytic fungus *Xylaria* sp. SNB-GTC2501. Tetrahedron Lett 56:4596–4598. doi:10.1016/j.tetlet.2015.06.022

Stinson AM, Zidack NK, Strobel GA et al (2003) Mycofumigation with *Muscodor albus* and *Muscodor roseus* for control of seedling diseases of sugar beet and *Verticillium* wilt of eggplant. Plant Dis 87:1349–1354. doi:10.1094/PDIS.2003.87.11.1349

Tarman K, Palm G, Wende K, Lindequist U (2011) Biological and chemical study of two Indonesian marine endophytic fungi. Planta Med 77:SL71. doi: 10.1055/s-0031-1282194

Trendowski M, Zoino JN, Christen TD et al (2015) Preparation, in vivo administration, dose-limiting toxicities, and antineoplastic activity of cytochalasin B. Transl Oncol 8:308–317. doi:10.1016/j.tranon.2015.06.003

Vicente MF, Basilio A, Cabello A, Peláez F (2003) Microbial natural products as a source of antifungals. Clin Microbiol Infect 9:15–32. doi:10.1046/j.1469-0691.2003.00489.x

Wang Y, Wang X, Lai G et al (2007) Three new sesquiterpenoids from the aerial parts of *Homalomena occulta*. Chem Biodivers 4:925–931. doi:10.1002/cbdv.200790081

Wang F, Fang Y, Zhang M et al (2008) Six new ergosterols from the marine-derived fungus *Rhizopus* sp. Steroids 73:19–26. doi:10.1016/j.steroids.2007.08.008

Webster J, Weber R (2007) Introduction to fungi, 3rd edn. Cambridge University Press, New York

Wei H, Xu YM, Espinosa-Artiles P et al (2015) Sesquiterpenes and other constituents of *Xylaria* sp. NC1214, a fungal endophyte of the moss *Hypnum* sp. Phytochemistry 118:102–108. doi:10.1016/j.phytochem.2015.08.010

Wells JM, Cutler HG, Cole RJ (1976) Toxicity and plant growth regulator effects of cytochalasin H isolated from *Phomopsis* sp. Can J Microbiol 22:1137–1143

Wicklow D, Rogers K, Dowd P, Gloer J (2011) Bioactive metabolites from *Stenocarpella maydis*, a stalk and ear rot pathogen of maize. Fungal Biol 115:133–142. doi:10.1016/j.funbio.2010.11.003

Wu S-H, Chen Y-W, Miao C-P (2011) Secondary metabolites of endophytic fungus *Xylaria* sp. YC-10 of *Azadirachta indica*. Chem Nat Compd 47:749–751. doi:10.1007/s10600-011-0086-z

Wu SH, He J, Li XN et al (2014) Guaiane sesquiterpenes and isopimarane diterpenes from an endophytic fungus *Xylaria* sp. Phytochemistry 105:197–204

Xu S, Hui MG, Yong CS et al (2009) Cytotoxic cytochalasin metabolites of endophytic *Endothia gyrosa*. Chem Biodivers 6:739–745. doi:10.1002/cbdv.200800034

Zhang Q, Xiao J, Sun QQ et al (2014) Characterization of cytochalasins from the endophytic *Xylaria* sp. and their biological functions. J Agric Food Chem 62:10962–10969. doi:10.1021/jf503846z