Natural Product Sciences
26(1) : 10-27 (2020)
https://doi.org/10.20307/nps.2020.26.1.10

<Review>

Endophytic Fungi Inhabiting Medicinal Plants and Their Bioactive Secondary Metabolites

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Abstract – Endophytes are defined as microorganisms that spend part of lifetime interior of plant tissues without causing negative effects. They have been used for agricultural purpose, biofuel production, bioremediation, medication, etc. In particular, endophytes have been emerged as a good source for bioactive secondary metabolites. A large number of secondary metabolites are currently being reported. In this report, we focus on the secondary metabolites that were originated from endophytic fungi inhabiting medicinal plants. They were classified into several groups such as nitrogenous compounds, steroids, sulfide-containing metabolites, terpenoids, polyketides, and miscellaneous for discussion of chemical structures and biological activities.
Keywords – Endophytic fungi, Secondary metabolites, Biological activities

Introduction

More than 300,000 secondary metabolites are presumed to be isolated from plants and more new derivatives are being continuously discovered up to date.[1] Plant metabolites have been used as a major source of medical and pharmaceutical area, and as precursor for chemical synthesis or structural modifications.[2] Specific microorganisms which live in surfaces or internal tissue of the plants are reported to induce changes in the plants' metabolomes.[3] Endophytes are microorganisms, which spend part of their lifetime interior of plant species without causing negative effects.[4] Endophytes are known to inhabit all over the plant tissues including leaves, stems, bark, and roots. Fungi and bacteria are most common type of endophytes. It was reported that economically important plants frequently yields novel species of endophytic fungi.[5,6] The studies of endophytic fungi could provide fundamental information on assessment about fungal diversity and distribution.[7] Plants are deeply related with the growth of endophytic fungi since endophytic fungi use a lot of mechanisms to adapt to their habitat environment.[8] Endophytes are known to help host plants increase competitiveness and productivity by improving resistance to environmental stress, protecting from herbivores and pathogens.[9] Recently, endophytic fungi isolated from plants have been paid attention to and have been studied for their functions.[9] In particular, these studies have been focused on secondary metabolites which could be used in the medical, pharmaceutical, agricultural, and environmental fields.[9]

Some endophytes have been reported to produce the same compounds as the host plants (Fig. 1), which might be caused by biosynthetic gene transfer from plants to endophytes or vice versa. For example, *Taxomyces andreanea*, an endophytic fungus isolated from bark of *Taxus brevifolia* which anticancer agent, paclitaxel (taxol®) was isolated from, was also found to produce the same compound, paclitaxel as the host plant.[10] This research suggested that endophytes from medicinal plants could be good producers for pharmaceutical agents instead of the original host plants.[11] Further studies to investigate endophytes that produce paclitaxel have been performed for various endophytes, including genera of *Taxomyces*, *Alternaria*, *Fusarium*, and *Pestalotiopsis*.[11] Vinblastine, an anticancer agent, was reported to be also produced by an endophytic fungus, *Alternaria* sp. isolated from *Catharanthus roseus*, the original plant for vinblastine to be first isolated.[12] In addition, the plant *Podophyllum peltatum* where podophyllotoxin, a lead compound of clinically available anticancer agents, etoposide and teniposide, was originally isolated from, was also investigated to see if its endophytes also produce the same compound as the plant.[13] In result its endophytes including the genera *Diphylleia*, *Dysosma*, and *Sinopodophyllum*

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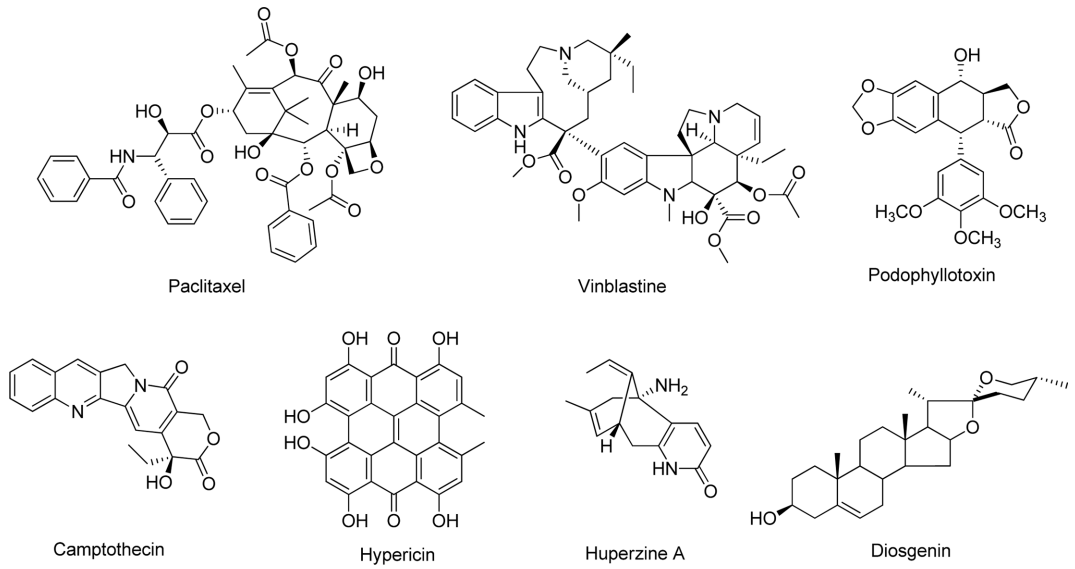

Fig. 1. Examples of pharmaceutical lead compounds produced by host plants and their endophytes.

also produced podophyllotoxin as the host plant.[13] These host-microbe chemical interactions were also found in many medicinal plants and their endophytes. Camptothecin, a clinically available anti-neoplastic agent, was produced by not only the plant *Camptotheca acuminate* but its endophytic fungus *Fusarium* solani.[14] In addition, bioactive secondary metabolites such as huperizine A, diosgenin, and hypericin, originally isolated from the plants *Huperzia serrata*, *Paris polyphylla*, and *Hypericum perforatum* were also found to be produced by their respective endophytes.[15-17]

In this review, we categorized the endophytic metabolites by chemical structures and discussed their occurrences and biological activities. It would help understand chemical properties and biological activities of secondary metabolites produced by endophytic fungi for drug discovery.

All the metabolites discussed in this review were listed depending on their original fungal strain and the medicinal plants where the endophytes were isolated Table 1. In addition, chemical structures of those secondary metabolites were also categorized into nitrogenous compounds, steroids, sulfide-containing metabolites, terpenoids, polyketides, and miscellaneous (Figs. 2-6).

Nitrogenous compounds

The nitrogen-containing organic compounds have been reported to be produced by endophytic fungi (Fig. 2). Among them, peptides are one of the major classes that are produced by microorganisms including bacteria and fungi. A cyclicpeptide, leucinostatin A (**1**) was isolated from cultures of an endophytic fungus *Acremonium* sp., inhabiting medicinal plant *Taxus baccata* and it inhibited growth of prostate cancer cell.[18] Cryptocandin (**2**), isolated from an endophytic fungus *Cryptosporiopsis quercina* residing in *Tripterygium wilfordii*, exhibited antifungal activity against *Botrytis cinerea*, *Candida albicans*, *Sclerotinia sclerotiorum*, and *Trichophyton* spp.[19] L-671,329 (**3**) obtained from *Cryptosporiopsis* sp. isolated from *Pinus sylvestris* showed inhibitory activity against glucan synthase and antifungal activities against *Aspergillus* spp., *C. albicans*, and *Saccharomyces cerevisiae*.[20] Cycloaspeptide A (**4**), isolated from *Penicillium raistrickii* inhabiting *T. brevifolia*, showed cytotoxic activity against human lung fibroblasts.[21] Tenuazonic acid (**5**), isolated from *Alternaria alternata* inhabiting *Indigofera enneaphylla*, exhibited antibacterial activity against *Mycobacterium tuberculosis* and inhibited ribosomal protein synthesis.[22] 16α-hydroxy-5-N-acetyl-ardeemin (**6**), isolated from *Aspergillus terreus* residing in *A. annua*, indicated acetylcholineesterase inhibitory activity.[23] Asperfumoid (**7**), isolated from *Aspergillus fumigatus* inhabiting *Cynodon dactylon*, showed antifungal activity against *C. albicans*.[24] Chaetoglobosins A (**8**) and C (**9**), isolated from *Chaetomium globosum* derived from *Ginko biloba*, revealed antifungal activity against *Mucor miegei*.[25] 2-Phenylethyl-1H-indol-3-yl-acetate (**10**) and 4-hydroxy-benzamide (**11**), isolated from *Colletotrichum gloeosporioides* residing in *Michelia champaca*, exhibited antifungal activities against *Clados-*

Table 1. Bioactive secondary metabolites produced by endophytic fungi inhabiting different medicinal plants

No.	Fungal endophyte	Host (medicinal plant)	Compounds	Biological activities	References
1	*Acremonium sp.*	*Taxus baccata*	Leucinostatin A (**1**)	Inhibition of prostate cancer cell growth	[18]
2	*Alternaria alternata*	*Indigofera enneaphylla*	Tenuazonic acid (**5**)	Antibacterial against *Mycobacterium tuberculosis* Inhibition of ribosomal protein synthesis	[22]
3	*Alternaria sp.*	*Polygonum senegalense*	Altenuene (**94**) 2-Epialtenuene (**95**)	Cytotoxic activity	[77]
4	*Alternaria sp.*	*Trixis vauthieri*	Altenusin (**117**)	Antifungal against *Paracoccidioides brasiliensis* Inhibition of trypanothione reductase	[95][96]
5	*Alternaria sp.*	*P. senegalense*	Alternariol (**96**)	Cytotoxic activity Inhibition of protein kinase and xanthine oxidase Induction of cell death of human colon carcinoma cells Induction of cytochrome P450 1A1 and apoptosis in murine heptatoma	[77-80]
6	*Alternaria sp.*	*P. senegalense*	Alternariol 5-*O*-methyl ether (**97**)	Cytotoxic activity Induction of cytochrome P450 1A1 and apoptosis in murine heptatoma	[77][80]
7	*Ampelomyces sp.*	*Urospermum picroides*	3-*O*-Methylalaternin (**105**)	Antibacterial against *Staphylococcus aureus*, *Staphylococcus epidermis*, and *Enterococcus faecalis*	[87]
8	*Ampelomyces sp.*	*U. picroides*	Altersolanol A (**106**)	Inhibition of bacterial growth	[85]
9	*Annulohypoxylon truncatum*	*Z. caduciflora*	Annulohpoxylotols A-B (**54-55**)	Inhibition of NF-κB activity	[42]
10	*A. truncatum*	*Z. caduciflora*	Xylariphilone (**149**)	Anti-inflammatory activity	[109]
11	*A. truncatum* *Colletotrichum sp.*	*Z. caduciflora* *Artemisia annua*	3-Oxo-ergosta-4,6,8(14),22-tetraene (**31**)	Antibacterial against *Pseudomonas* sp., *Bacillus subtilis*, *Sarcina lutea, and S. aureus* Antifungal against *Aspergillus niger*, *Candida albicans*, *Phytophthora capisici*, *Gaeumannomyces graminis*, *Rhizoctonia cerealis*, and *Helminthosporium sativum* Inhibition of NF-κB activity	[42][43]
12	*Aspergillus terreus*	*A. annua*	16α-Hydroxy-5-N-acetyl-ardeemin (**6**)	Acetylcholineesterase inhibitory activity	[23]
13	*Aspergillus clavatus* *Paecilomyces sp.*	*Tectona grandis* *Taxus mairei* *Torreya grandis*	Brefeldin A (**150**)	Antifungal against *A. niger*, *C. albicans*, and *Trichophyton rubrum* Anticancer (human lung cancer cell line Spc-A-1)	[108]
14	*Aspergillus flocculus* *A. niger* *Aspergillus sp.* *Chaetomium sp.* *Fusarium sp.* *Lachnum abnorme* *Mycoleptodiscus sp.* *Nodulisporium sp.* *Pestalotiopsis uvicola*	*Markhamia platycalyx* *Cynodon dactylon* *Callistemon subulatus* *Huperzia serrata* *Piper guineense* *Ardisia cornudentata* *Piper sintenense* *Dittrichia viscosa* *Artemisia japonica*	Ergosterol (**30**)	Antibacetrial against *Escherichia coli*, *Bacillus megaterium, S. lutea,* and *S. aureus* Antifungal against *C. albicans* and *Microbotryrum violaceum* Anti-*Helicobacter pylori* activity	[39-41][44]

Table 1. continued

No.	Fungal endophyte	Host (medicinal plant)	Compounds	Biological activities	References
15	*A. fumigatus*	*Cynodon dactylon*	Asperfumin (**107**) Asperfumoid (**7**) Physcion (**108**)	Antifungal against *C. albicans*	[24]
16	*A. niger*	*C. dactylon*	Aurasperone A (**99**) Rubrofusarin B (**100**)	Strong co-inhibitors on xanthine oxidase, colon cancer cell, and some microbial pathogens	[83]
17	*A. niger*	*C. dactylon*	Helvolic acid (**75**) Monomethylsulochrin (**115**)	Antibacterial against *S. lutea* and *S. aureus* Antifungal against *C. albicans Anti-Helicobacter pylori*	[39][40]
18	*Aspergillus parasiticus*	*Sequoia sempervirens*	Sequoiatones A-B (**151-152**)	Anticancer (breast cancer cell line)	[109]
19	*A. parasiticus*	*S. sempervirens*	Sequoiatones C-F (**153-156**)	Brine shrimp lethality activity	[110]
20	*Botryosphaeria sp.*	*Maytenus hookeri*	CJ-14445 (**66**)	Antifungal against *C. albicans*, *Saccharomyces cervisiae*, and *Penicillium avellaneum*	[58]
21	*Cephalosporium sp.* *Microsphaeropsis olivacea*	*Trachelospermum jasminoides* *Pilgerodendron uviferum*	Graphislactone A (**98**)	Antioxidant activity	[81][82]
22	*Chaetomium globosum*	*Ginko biloba*	Chaetoglobosins A (**8**) and C (**9**)	Antifungal against *Mucor miegei*	[25]
23	*Chalara sp.*	*Artemisia vulgaris*	Isofusidienol A-D (**101-104**)	Antibacterial against *B. subtilis*, *E. coli*, and *S.aureus* Antifungal against *C. albicans*	[84]
24	*Choridium sp.*	*Azadirachta indica*	Javanicin (**109**)	Antibacterial against *Pseudomonas aeruginose* and *Pseudomonas fluorescens*	[86]
25	*Colletotrichum gloeosporioides*	*Aquilaria sinensis*	(3*R*,6*E*,10*S*)-2,6,10-Trimethyl-3-hydroxydodeca-6,11-diene-2,10-diol (**56**) Colletotricole A (**51**) Colletotricone A (**138**) Nigrosporanenes A-B (**139-140**) Phenethyl 2-hydroxypropanoate (**121**) 2-(4-Methylthiazol-5-yl) ethyl 2-hydroxy propanoate (**52**) Phthalic acid diisobutyl ester (**122**)	Growth inhibition (tumor cell lines MCF-7, NCI-H460, HepG-2, and SF-268)	[51]
26	*C. gloeosporioides*	*Michelia champaca*	2-(4-Hydroxyphenyl)acetic acid (**118**) 2-(2-Hydroxyphenyl)acetic acid (**119**) 2-Phenylethyl 1H-indol-3-yl-acetate (**10**) 4-Hydroxy-benzamide (**11**)	Antifungal against *Cladosporium cladosporioides* and *Cladosporium sphaerospermum*	[26]
27	*C. gloeosporioides*	*Artemisia mongolica*	Colletotric acid (**120**)	Antibacterial against *B. subtilis*, *S. aureus*, and *S. lutea* Antifungal against *H. sativum*	[100]
28	*C. gloeosporioides*	*Piper nigrum*	Piperine (**12**)	Antibacterial, antifungal, anti-inflammatory, antioxidant, antidepressant, antitumor, antipyretic, anticonvulsant, cytotoxic, hepato-protective, insecticidal, and immuno-modulatory activities	[27]

Table 1. continued

No.	Fungal endophyte	Host (medicinal plant)	Compounds	Biological activities	References
29	*Colletotrichum sp.*	*A. annua*	(22*E*,24*R*)-6-acetoxy-ergosta-7,22-dien-3β,5α,6β-triol (**33**) (22*E*,24*R*)-3,6-diacetoxy-ergosta-7,22-dien-3β,5α,6β-triol (**34**) (22*E*,24*R*)-3-acetocy-6-phenylacetyloxy-ergosta-7,22-dien-3β,5α,6β-triol (**35**)	Antibacetrial against *B. subtilis*, *B. megaterium, E. coli, Pseudomonas* sp., *S. lutea,* and *S. aureus* Antifungal against *A. niger*, *C. albicans*, *P. capisici*, *G. graminis*, *R. cerealis*, *H. sativum*, and *M. violaceum*	[43][45]
30	*Colletotrichum sp.*	*A. annua*	(22*E*,24*R*)-3-acetoxy-19(10 → 6)-abeo-ergosta-5,7,9,22-tetraen-3β-ol (**36**) (22*E*,24*R*)-19(10 → 6)-beoergosta-5,7,9,22-tetraen-3β-ol (**37**) Ergosterone (**38**)	Antifungal against *M. violaceum* Antibacetrial against *E. coli* and *B. megaterium*	[45]
31	*Colletotrichum sp.* *Cordyceps ninchukispora* *Fusarium chlamydosporium* *Mollisia sp.*	*A. annua* *Beilschmiedia erythrophloia* *Anvillea garcinii* *A. cornudentata*	Ergone (**39**)	Antibacetrial against *E. coli* and *B. megaterium* Antifungal against *M. violaceum* Anti-inflammatory activity	[28][43-46]
32	*Colletotrichum sp.* *Gaeumannomyces sp.* *Mollisia sp.*	*A. annua* *Santalum album* *Phragmites communis* *A. cornudentata*	Ergosterol peroxide (**40**)	Antibacterial against *E. coli, B. megaterium, B. subtilis, Pseudomonas* sp., *S. lutea,* and *S. aureus* Antifungal against *A. niger*, *C. albicans*, *G. graminis*, *H. sativum*, *M. violaceum*, *P. capisici*, and *R. cerealis* Cytotoxicy activity Nitric oxide (NO) reduction activity	[43][45-47]
33	*Colletotrichum sp.*	*A. annua* *H. serrata*	Ergost-5-en-3β-ol (**41**)	Antibacterial against *Pseudomonas* sp. and *B. subtilis* Antifungal against: *P. capisici, G. graminis, R. cerealis,* and *H. sativum*	[43]
34	*Colletotrichum sp.*	*Morus alba*	Evariquinone (**110**)	Neuroprotective activity	[87]
35	*C. ninchukispora*	*B. erythrophloia*	Cordycepiamides A (**13**), B (**14**), and D (**15**)	Inhibition of IL-6 in LPS activated RAW 264.7 cell	[28]
36	*Cryptosporiopsis quercina*	*Tripterygium wilfordii*	Cryptocandin (**2**)	Antifungal against *C. albicans*, *Trichophyton* spp., *Sclerotinia sclerotiorum*, and *Botrytis cinerea*	[19]
37	*C. quercina*	*T. wilfordii*	Cryptocin (**16**)	Antifungal against *Pleomorphomonas oryzae*	[29]
38	*Cryptosporiopsis sp.*	*Pinus sylvestris*	L-671,329 (**3**)	Antifungal against *Aspergillus* spp., *C. albicans*, and *S. cerevisiae* Inhibitition of glucan synthase	[20]
39	*Edenia sp.*	*Petrea volubilis*	Palmarumycin CP17 (**123**) Palmarumycin CP18 (**124**)	Inhibition of growth of the *Leishmania donovani*	[98]
40	*Emericella sp.*	*Astrgalus lentiginosus*	Secoemestrin D (**50**)	Cytotoxic activity	[50]
41	*Epichloe typhina*	*Phleum pratense*	Chokol A (**53**) Gamagonolide A (**157**)	Antifungal against *Cladosporium phlei*	[52][111]

Table 1. continued

No.	Fungal endophyte	Host (medicinal plant)	Compounds	Biological activities	References
42	*Eupenicillium sp.*	*Xanthium sibiricum*	(2*S*)-Butylitaconic acid (**158**) (2*S*)-Hexylitaconic acid (**159**)	Antibacterial against *Acinetobacter* sp.	[112]
43	*Eupenicillium sp.*	*X. sibiricum*	Eupenicinicol B (**160**)	Antibacterial against *S. aureus*	[112]
44	*Eupenicillium sp.*	*Murraya paniculata*	Alantryleunone (**17**) Alantryphenone (**18**) Alantrypinene B (**19**)	Insecticide	[30]
45	*Eutypella scoparia*	*Garcinia dulcis*	Scoparasin B (**20**)	Antifungal against *Microsporum gypseum*	[31]
46	*Fusarium sp.*	*Selaginella pallescens*	CR377 (**79**)	Antifungal against *C. albicans*	[71]
47	*Fusarium subglutinans*	*T. wilfordii*	Subglutinols A (**67**) and B (**68**)	Immunosuppressive activity	[59]
48	*Gaeumannomyces sp.*	*P. communis*	1-*O*-Methyl-6-*O*-(α-D-ribofuranosyl)-emodin (**111**)	Nitric oxide (NO) reduction activity	[28]
49	*Gaeumannomyces sp.*	*P. communis*	1-*O*-Methylemodin (**112**)	Antifungal against *Phellinus tremulae* Nitric oxide (NO) reduction activity Inhibition of IL-625 secretion, protein tyrosine phosphatase 1B, and acetylcholinesterase	[88-91]
50	*Gaeumannomyces sp.*	*P. communis*	5α,8α-Epidioxy-(22*E*,24*R*)-23-methylergosta-6,22-dien-3β-ol (**42**) 5α,8α-Epidioxyergosta-,9(11),22-trien-3-ol (**43**) Stemphols C (**125**) and D (**126**)	Nitric oxide (NO) reduction activity Immune-modulatory activity	[28]
51	*Hormonema dematioides*	*Abies balsamea*	Rugulosin (**114**)	Cytotoxic activity Hepatocarcinogenesis to mice and rats Fatty degeneration, liver cell necrosis	[92][93]
52	*Hormonema sp.*	*Juniperus communis*	Enfumafungin (**76**)	Antifungal against *C. albicans*, *C. tropicalis*, *Aspergillus flavus*, *A. fumigatus*, and *Saccharomyces cerevisiae* Inhibitor of fungal cell wall glucan synthesis.	[66-67]
53	*Massrison sp.*	*Rehmannia glutinosa*	Massarigenin D (**161**) Arthropsolide A (**162**) Spiromassaritone (**163**)	Antifungal against *Cryptococcus neoformans*, and *T. rubrum*	[113]
54	*Mollisia sp.*	*A. cornudentata*	Emodin (**113**)	Inhibition of IL-6 in LPS activated RAW 264.7 cell	[46]
55	*Mycoleptodiscus sp.*	*Tinospora crispa*	7-Epiaustdiol (**164**)	Antioomycetes against *Aphanomyces cochlioides* and *Phytophthora sojae*	[114]
56	*Neosartorya fischeri*	*Glehnia littoralis*	Fischerin (**21**)	Neuroprotective activity	[32]
57	*Neotyphodium uncinatum*	*Festuca pratensis*	Loline (**22**)	Anti-insect activity Anti-aphid activity	[33]
58	*Nodulisporium sp.*	*Juniperus cedrus*	Nodulosporins A-B (**127-128**)	Antifungal against *Microbotryium violaceum*	[99]
59	*Nodulisporium sp.*	*Erica arborea*	Nodulosporins D-F (**129-131**)	Antibacterial against *B. megaterium* Antifungal against *M. violaceum* Anti-algal against *Chlorella fusca*	[100][101]

Table 1. continued

No.	Fungal endophyte	Host (medicinal plant)	Compounds	Biological activities	References
60	*Penicillium brevicompactum*	*Taxus brevifolia*	Mycophenolic acid (**132**)	Antibacterial against *B. subtilis*, *Xanthomonas begoniae*, *Actinomyces scabies* Antifungal against *Claviceps purpurea*, *Penicillium erythroseptica*, *Rhizoctonia crocorum*, *R. solani*, *Stereum purpureum*, and *Verticillium dahliae* Antiviral activity Antitumor activity Immunosuppressive activity Antipsoriatic activity	[102]
61	*Penicillium raistrickii*	*T. brevifolia*	Cycloaspeptide A (**4**)	Cytotoxic activity	[21]
62	*P. raistrickii*	*T. brevifolia*	Fiscalin A-C (**23-25**)	Inhibition of binding of radiolabeled substance P ligand to the human neurokinin (NK-1)	[34]
63	*P. raistrickii*	*T. brevifolia*	Pseurotin A (**26**)	Antibacterial against *Erwinia carotovora* and *Pseudomonas syringae* Induction of cell differentiation of PC12 neuronal cells	[35]
64	*Penicillium sp.*	*T. brevifolia*	Phomopsolides A-B (**80-81**)	Antibacterial against *Staphylococcus aureus*	[72]
65	*Penicillium sp.*	*T. brevifolia*	Phomopsolide C-E (**82-84**)	Antibacterial against *S. aureus* and *Vibrio harveyii* Antifeeding activity	[73]
66	*Penicillium sp.*	*Melia azedarach*	Preaustinoids A-B (**69-70**)	Antibacterial against *E. coli*, *S. aureus*, *P. aeruginosa*, *Bacillus* sp.	[60]
67	*Periconia sp.*	*Taxus cuspidate*	Periconicins A (**71**)	Antibiotic activity	[61]
68	*Periconia sp.*	*T. cuspidate*	Periconicins B (**72**)	Antifungal against *C. albicans*, *Trichophyton mentagrophytes*, and *T. rubrum*	[62]
69	*Pestalotiopsis microspora*	*Terminalia morobensis*	Pestacin (**133**) Isopestacin (**134**)	Antioxidant activity	[103]
70	*Pezicula livida*	*Fagus sylvatica*	(*R*)-Mellein (**27**)	Antibacterial against *B. megaterium*, *E. coli* Antifungal against *Ustilago violacea*, *Eurotium repens*, and *Cercospora fusca*	[75]
71	*Phaeospheria sp.*	*Echinacea purpurea*	Porritoxin (**128**)	Antitumor activity	[36]
72	*Phoma medicaginis*	*Medicago sativa*	Brefeldine A (**150**)	Antibiotic activity Initiation of apoptosis in cancer cells	[115]
73	*Phoma sp.*	*Artemisia princeps*	(3*S*,4*S*)-3,8-Dihydroxy-6-methoxy-3,4,5-trimethylisochroman-1-one (**92**) (3*R*,4*S*)-3,8-Dihydroxy-3-hydroxymethyl-6-methoxy-4,5-dimethylisochroman-1-one (**93**)	Nitric oxide (NO) reduction activity	[76]
74	*Phoma sp.*	*P. communis*	Barceloneic acid C (**135**)	Antibacterial against *Listeria monocytogenes* and *Staphylococcus pseuditermedius*	[104]
75	*Phoma sp.*	*Kandelia candel*	Epicorazines A-C (**45-47**) Exserohilone A (**48**) Phomazine B (**49**)	Cytotoxic activity : HL-60, HCT-116, K562, MGC-803, and A549 cell lines	[49]

Table 1. continued

No.	Fungal endophyte	Host (medicinal plant)	Compounds	Biological activities	References
76	*Phoma sp.*	*S. albicans*	Macrophic acid (**85**) Phomones C-F (**86-89**) Rosellisin (**90**)	Cytotoxic activity	[74]
77	*Phomopsis cassiae*	*Cassia spectabilis*	3,12-Dihydroxycadalene (**57**)	Antifungal against *C. cladosporioides* and *C. sphaerospermum*	[53]
78	*Phomopsis phaseoli* *Melanconium betulinum*	*Betula pendula*	3-Hydroxypropionic acid (**166**)	Nematoicidal activity against *Meloidogyne incognita*, *Caenorhabditis elegans*	[116]
79	*Phomopsis sp.*	*Urobotrya siamensis* *Grewia sp.* *Mesua ferrea* *Rhododendron ciliicalyx* *Tadehagi sp*	3-Nitropropionic acid (**29**)	Antibacterial against *Mycobacerium tuberculosis* Inhibition of enzyme succinate dehydrogenase in mitochondria	[38]
80	*Phomopsis sp.*	*Salix gracilostyla*	Phomopsichalasin (**28**)	Antibacterial against *B. subtilis, S. aureus,* and *Salmonella gallinarum* Antifungal against *C. tropicalis*	[97]
81	*Phomopsis sp.*	*Erythrina cristagalli*	Mevinic acid (**167**)	Anti-inflammatory activity	[117]
82	*Phomopsis sp.*	*E. cristagalli*	Phomol (**168**)	Antibacterial against *Arthrobacter citreus*, *Corynebacterium insidiosum*, and *P. fluorescens* Antifungal against *Absidia glauca*, *Ascocyta pisi*, *Paecilomyces variotii*, *Penicillium islandicum*, *Penicillium notatum*, and *Zygorhynchus moelleri* Antiinflammatory and Cytotoxic activity	[117]
83	*Phyllosticta sp.*	*A.balsamea*	Heptelidic acid (**77**)	Antimalarial activity Inhibition of mammalian DNA polymerases β and γ Induction of etoposide-induced apoptosis in leukemia cells	[68][69]
84	*Phyllosticta spinarum*	*Platycladus orientalis*	Tauranin (**73**)	Anticancer (non-small cell lung cancer, breast cancer, CNS cancer-glioma, metastatic prostate cancer, and pancreatic carcinoma)	[63]
85	*Rhizoctonia solani*	*Cyperus rotundus*	Solanioic acid (**44**)	Antibacterial against methicillin-resistant *S. aureus*	[48]
86	*Rhizoctonia sp.*	*C. dactylon*	Rhizoctonic acid (**116**)	Anti-*Helicobacter pylori*	[94]
87	*Trichoderma harzianum*	*Ilex cornuta*	Trichodermin (**78**)	Plant growth regulation	[70]
88	*Trichoderma koningiopsis*	*Panax notoginseng*	Koningiopisins A-H (**141-148**)	Antibacterial against *Bacillu anthracis*, *E. faecalis*, *Enterococcus faecium*, *S. aureus*, *Staphylococcus simulans*, *S. epidermis*, *Streptococcus pneumoniae*, *L. monocytogenes*, and *Shigella dysenteriae* Antifungal against *Plectosphaerella cucumerina*, *Fusarium solani*, *F. oxysporum*, and *Alternaria panax*	[106]
89	*Tubercularia sp.*	*T. mairei*	Tubercullariols A-C (**58-60**)	Antitumor (cervical cancer cell line)	[54]

Table 1. continued

No.	Fungal endophyte	Host (medicinal plant)	Compounds	Biological activities	References
90	*Xylaria sp.*	*Licuala spinosa*	1α-10α-Epoxy-7α-hydroxyeremophil-11-en-12,8-βolide (**61**)	Antifungal against *C. albicans* Antiparasitic activity	[55]
91	*Xylaria sp.*	*Abies holophylla*	Griseofulvin (**136**) Dechlorogriseofulvin (**137**)	Antifungal against *Alternaria mali*, *B. cinerea*, *C. gloeosporioides*, *Corticium sasaki*, *F. oxysporum*, and *Magnaporthe grisea*	[105]
92	*Xylaria sp.*	*Piper aduncum*	Phomenone (**62**)	Antifungal against *C. cladosporioides* and *C. sphaerospermum*	[56]
93	*Xylaria sp.*	*G. dulcis*	Sordaricin (**74**)	Antifungal against *C. albicans* and *Candida glabrata*	[64]
94	*Xylaria sp.*	*Torreya jackii*	Xylarenic acid (**63**) Xylarenones A-B (**64-65**)	Antitumor (cervical cancer cell line)	[57]

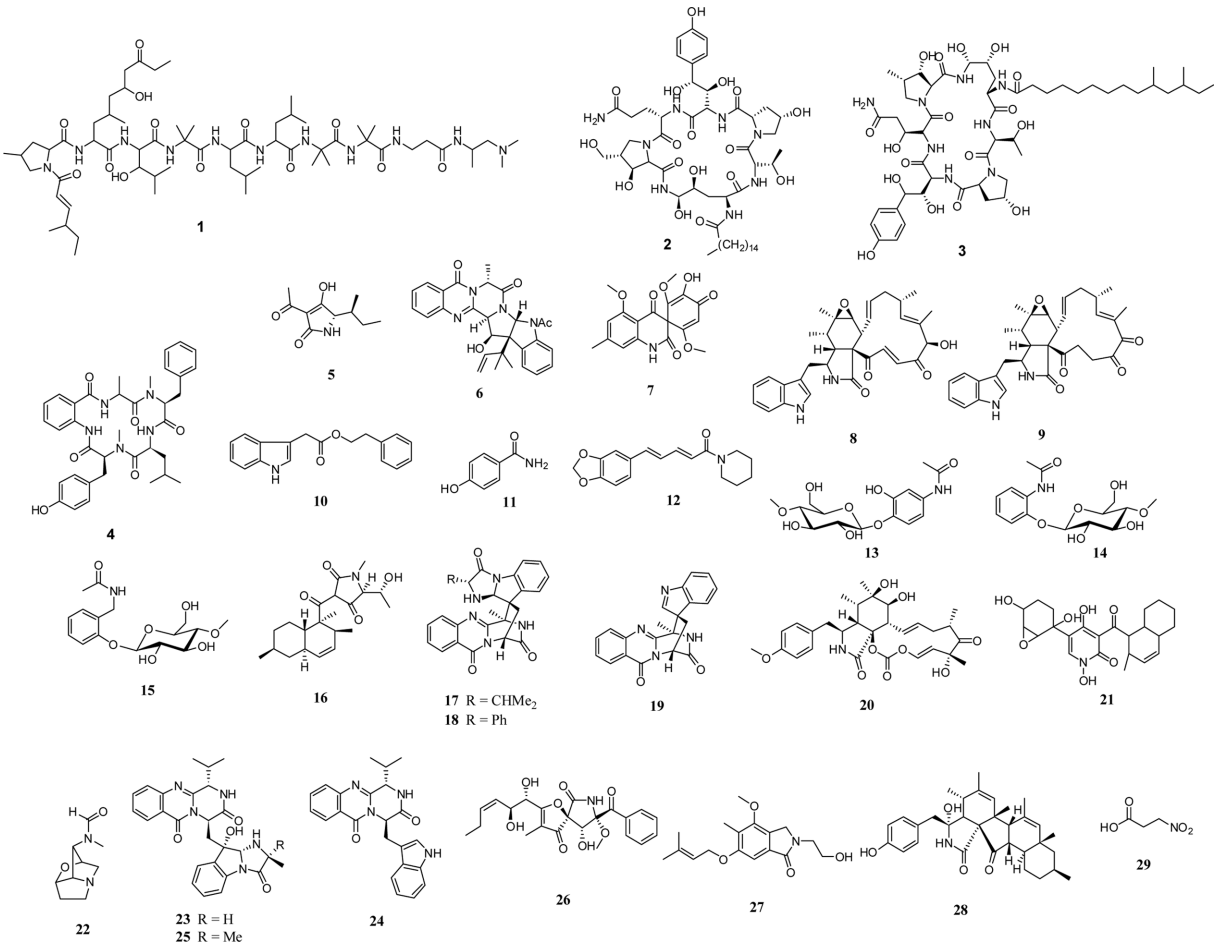

Fig. 2. Nitrogenous compounds produced by endophytic fungi.

porium cladosporioides and *C. sphaerospermum*.[26] Piperine (**12**), which is known as plant-derived compound, was also isolated from *C. gloeosporioides* inhabiting *Piper nigrum* and showed antibacterial, antifungal, anti-inflammatory, antioxidant, antidepressant, antitumor, anti-pyretic, anticonvulsant, cytotoxic, hepato-protective, in-secticidal, immuno-modulatory activities.[27] Cordycepiamides A (**13**), B (**14**), and D (**15**) isolated from *Cordyceps ninchukispora* derived from *Beilschmiedia erythrophloia*, revealed inhibition of IL-6 in LPS-activated RAW 264.7 cell.[28] Cryptocin (**16**), isolated from *Cryptosporiopsis quercina* residing in *T. wilfordii*, exhibited antifungal activity against *Pleomorphomonas oryzae*.[29] Alantryleunone (**17**), alantryphenone (**18**), and alantrypinene B (**19**), isolated from *Eupenicillium* sp. inhabiting *Murraya paniculata*, showed insecticidal activities.[30] Scoparasin B (**20**) was isolated from *Eutypella scoparia* derived from *Garcinia dulcis*. Scoparasin B exhibited antifungal activity against *Microsporum gypseum*.[31] Fischerin (**21**), isolated from *Neosartorya fischeri* residing in *Glehnia littoralis*, indicated potent neuroprotective activity.[32] Loline (**22**), isolated from *Neotyphodium uncinatum* inhabiting *Festuca pratensis*, showed anti-insect and anti-aphid activities.[33] Fiscalins A-C (**23-25**) and pseurotin A (**26**) were isolated from *P. raistrickii* derived from *T. brevifolia*. Fiscalins inhibited binding of radiolabeled substance P ligand to the human neurokinin (NK-1).[34] Pseurotin A induced cell differentiation of PC12 neuronal cells and exhibited antibacterial activities against *Erwinia carotovora* and *Pseudomonas syringae*.[35] Porritoxin (**27**), isolated from *Phaeospheria* sp. residing in *Echinacea purpurea*, indicated antitumor activity.[36] Phomopsichalasin (**28**), isolated from *Phomopsis* sp. inhabiting *Salix gracilostyla*, showed antimicrobial activities against *Bacillus subtilis*, *Staphylococcus aureus*, *Salmonella gallinarum*, and *Candida tropicalis*.[37] 3-Nitropropionic acid (**29**), isolated from *Phomopsis* sp. derived from *Urobotrya siamensis*, *Grewia* sp., *Mesua ferrea*, *Rhododendron ciliicalyx*, and *Tadehagi* sp., inhibited the enzyme succinate dehy-drogenase in mitochondria and showed antibacterial

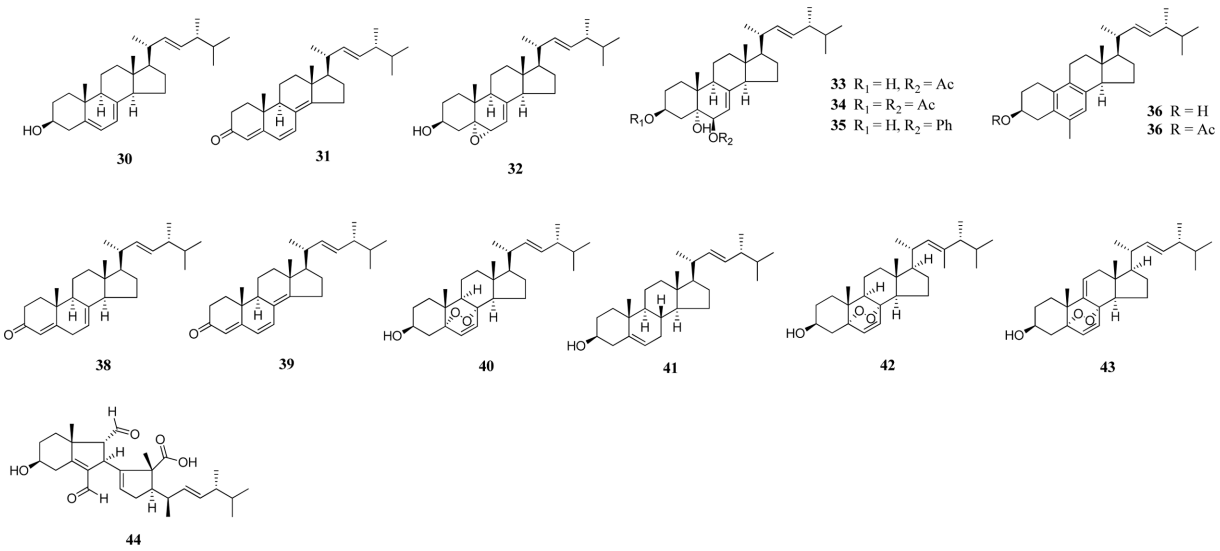

Fig. 3. Steroids produced by endophytic fungi.

activity against *Mycobacerium tuberculosis*.[38]

Steroids

Some steroids have been isolated from endophytic fungi as shown in Fig. 3. They are mostly ergosterol derivatives. Ergosterol (**30**) was isolated from most of fungi including endophytic fungi and it is known to have diverse biological activities anti-*Helicobacter pylori* activity and antimicrobial activities.[39-41] 3-Oxo-ergosta-4,6,8(14),22-tetraene (**31**) was isolated from an endophytic fungus *Annulohypoxylon truncatum* residing in *Zizania caduciflora* as well as *Colletotrichum* sp. in *A. annua*. **31** inhibited NF-κB activity and showed antimicrobial activities against *Pseudomonas* sp., *B. subtilis*, *Sarcina lutea*, *S. aureus*, *Aspergillus niger*, *C. albicans*, *Phytophthora capisici*, *Gaeumannomyces graminis*, *Rhizoctonia cerealis*, and *Helminthosporium sativum*.[42,43] (3β,5α,6α,22*E*)-3-Hydroxy-5,6-epoxy-7-one-8(14),22-dien-ergosta (**32**), isolated from *Chaetomium* sp. residing in *H. serrata*, inhibited acetylcholinesterase.[44] (22*E*,24*R*)-6-Acetoxy-ergosta-7,22-dien-3β,5α,6β-triol (**33**), (22*E*,24*R*)-3,6-diacetoxy-ergosta-7,22-dien-3β,5α,6β-triol (**34**), (22*E*,24*R*)-3-acetocy-6-phenylacetyloxy-ergosta-7,22-dien-3β,5α,6β-triol (**35**), (22*E*, 24*R*)-3-acetoxy-19(10→6)-abeo-ergosta-5,7,9,22-tetraen-3β-ol (**36**), (22*E*,24*R*)-19(10→6)-abeoergosta-5,7,9,22-tetraen-3β-ol (**37**), and ergosterone (**38**) with antimicrobial activities were also isolated from *Colletotrichum* sp. inhabiting *Artemisia annua*. Ergone (**39**) was isolated from *Colletotrichum* sp., *C. ninchukispora*, *F. chlamydosporium*, and *Mollisia* sp. derived from *A. annua*, *B. erythrophloia*, *Anvillea garcinii*, *A. cornudentata*, respectively. Ergone exhibited anti-inflammatory activity and antimicrobial activities against *E. coli*, *B. megaterium*, and *M. violaceum*.[28,43,45,46] Ergosterol peroxide (**40**) is another common steroid produced by fungi together with ergosterol. **40** exhibited diverse biological activities so far, including nitric oxide (NO) reduction, cytotoxicity, and antimicrobial activities.[43-47] Ergost-5-en-3β-ol (**41**), isolated from *Colletotrichum* sp. residing in *A. annua* and *H. serrata*, indicated antimicrobial activities against *Pseudomonas* sp., *B. subtilis*, *P. capisici*, *G. graminis*, *R. cerealis*, *H. sativum*.[43] 5α,8α-Epidioxy-(22*E*,24*R*)-23-methylergosta-6,22-dien-3β-ol (**42**), isolated from *Gaeumannomyces* sp. inhabiting *P. communis*, showed nitric oxide (NO) reduction, anti-inflammatory, and immune-modulatory activities.[28] 5α,8α-Epidioxyergosta-6,9(11),22-trien-3-ol (**43**), isolated from *Gaeumannomyces* sp. and *Mollisia* sp. derived from *P. communis* and *A. cornudentata*, exhibited nitric oxide (NO) reduction activity.[28,46] Solanioic acid (**44**), a degraded and rearranged steroid, was isolated from cultures of *Rhizoctonia solani* derived from *Cyperus rotundus* and it showed antibacterial activity against methicillin-resistant *S. aureus*.[48]

Sulfur-containing metabolites

Some sulfur-containing metabolites have been isolated from endophytic fungi as shown in Fig. 4. Five thiodiketopiperizines, epicorazines A-C (**45** - **47**), exserohilone A (**48**), and phomazine B (**49**), were isolated from an endophytic fungus *Phoma* sp. residing in *Kandelia*

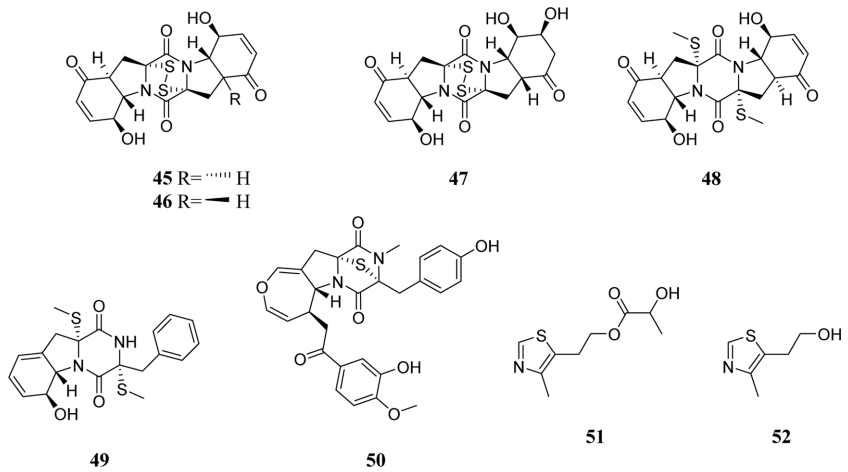

Fig. 4. Sulfur-containing compounds from endophytic fungi.

candel. These metabolites exhibited cytotoxicity against HL-60, HCT-116, K562, MGC-803, and A549 cell lines.[49] The biosynthetic pathways for dithiodiketopeperazines were investigated. Two amino acids were coupled with amide bond and cyclized to form diketopiperazine. And then sulfur donated from methionine, cycteine, etc was known to be incorporated into the diketopiperazines.[50] Secoemestrin D (**50**), obtained from *Emericella* sp. derived from *Astrgalus lentiginosus*, also showed cytotoxic activity.[51] Colletotricole A (**51**) and 2-(4-methylthiazol-5-yl)Ethyl 2-hydroxy propanoate (**52**), isolated from *C. gloeosporioides* in *Aquilaria sinensis*, inhibited growth of tumor cell lines MCF-7, NCI-H460, HepG-2, and SF-268.[52]

Terpenoids

Terpenoids also have been reported to be produced by endophytic fungi as shown in Fig. 5. Chokol A (**53**), isolated from *Epichloe typhina* residing in *Phleum pretense*, showed antifungal activity against *Cladosporium phlei*.[53] Annulohpoxylotols A (**54**) and B (**55**), obtained from *A. truncatum* in *Z. caduciflora*, showed inhibition of NF-κB activity.[42] (3*R*,6*E*,10*S*)-2,6,10-trimethyl-3-hydroxydodeca-6,11-diene-2,10-diol (**56**), isolated from *C. gloeosporioides* in *A. sinensis*, exhibited growth inhibition of tumor cell lines MCF-7, NCI-H460, HepG-2, and SF-268.[52] 3,12-Dihydroxycadalene (**57**), isolated from *Phomopsis cassiae* residing in *Cassia spectabilis*, showed antifungal activities against *C. cladosporioides* and *C. sphaerospermum*.[54] Tubercullariols A-C (**58**-**60**), obtained from *Tubercularia* sp. derived from *Taxus mairei*, showed antitumor activities against cervical cancer cell line.[55] 1α-10α-Epoxy-7α-hydroxyeremophil-11-en-12,8-βolide (**61**), isolated from *Xylaria* sp. in *Licuala spinosa*, exhibited not only antifungal activity against *C. albicans* but also antiparasitic acitivity.[56] Phomenone (**62**), isolated from *Xylaria* sp. residing in *Piper aduncum*, showed antifungal activities against *C. cladosporioides* and *C. sphaerospermum*.[57] Xylarenic acid (**63**), xylarenones A (**64**), and B (**65**) obtained from *Xylaria* sp. derived from *Torreya jackii*, showed antitumor activities about cervical cancer cell line.[58] CJ-14445 (**66**), isolated from *Botryosphaeria* sp. inhabiting *Maytenus hookeri*, exhibited antifungal activity against *C. albicans*, *S. cervisiae*, and *Penicillium avellaneum*.[59] Subglutinols A (**67**) and B (**68**) isolated from *Fusarium subglutinans* residing in *Tripterygium wilfordii* indicated potent immunosuppressive activity.[60] Preaustinoids A (**69**) and B (**70**), obtained from *Penicillium* sp. derived from *Melia azedarach*, showed antibacterial activities against *Bacillus* sp., *E. coli*, *S. aureus*, and *Pseudomonas aeruginosa*.[61] Periconicins A (**71**) and B (**72**), isolated from *Periconia* sp. inhabiting *Taxus cuspidate*, exhibited antimicrobial activities against *C. albicans*, *Trichophyton mentagrophytes*, and *T. rubrum*.[62] Tauranin (**73**) isolated from *Phyllosticta spinarum* residing in *Platycladus orientalis* indicated anticancer activities against non-small cell lung cancer, breast cancer, CNS cancer-glioma, metastatic prostate cancer, and pancreatic carcinoma.[63] Sordaricin (**74**), obtained from *Xylaria* sp. derived from *Garcinia dulcis*, showed antifungal activities against *Candida glabrata* and *C. albicans*.[64] Helvolic acid (**75**), isolated from *A. niger* inhabiting *C. dactylon*, exhibited anti-*helicobacter pylori* activity as well as antimicrobial activities against *S. lutea*, *S. aureus*, and *C. albicans*.[39,40] Enfumafungin (**76**) isolated from

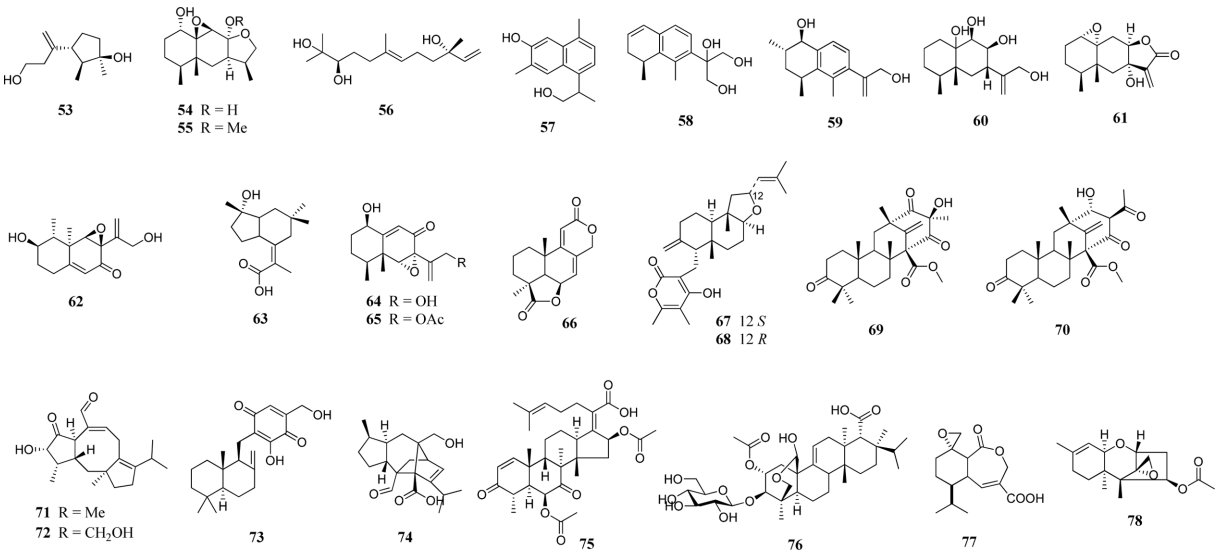

Fig. 5. Terpenoids produced by endophytic fungi.

Hormonema sp. residing in *Juniperus communis*, showed antifungal activities against *C. albicans*, *C. tropicalis*, *Aspergillus flavus*, *A. fumigatus*, and *S. cerevisiae* by inhibiting synthesis of glucan in fungal cell.[65-67] A sesquiterpene lactone, heptelidic acid (**77**), isolated from *Phyllosticta* sp. residing in *A. balsamea*, exhibited antimalarial activity and inhibited mammalian DNA polymerases β and γ as well as etoposide-induced apoptosis in leukemia cells.[68,69] Trichodermin (**78**), a member of 12,13-epoxytrichothecene mycotoxin, was characterized from *Trichoderma harzianum* living in *Ilex cornuta*. Trichodermin was reported to be a very potent inhibitor of eukaryotic protein synthesis, specifically by inhibiting peptide bond formation at the initiation stage of translation and by inhibiting peptidyl transferase activity required for translational elongation and/or termination.[70]

Polyketides

Polyketides are one of major secondary metabolites produced by endophytic fungi. Among polyketides, many pyranone-type compounds including monobenzopyranones, dibenzo-α-pyranones, and naphthopyranones have been reported to be isolated as shown in Fig. 6. CR377 (**79**) with antifungal activity against *C. albicans* was isolated from *Fusarium* sp. derived from *Selaginella pallescens*d.[71] Phomopsolides A-E (**80 - 84**) isolated from *Penicillium* sp. inhabiting *T. brevifolia* exhibited anti-feeding and antibacterial activity against *S. aureus*. Moreover, **82 - 84** showed antibacterial activity against *Vivrio harveyii*.[72,73] Macrophic acid (**85**), phomones C-F (**86 - 89**) and rosellisin (**90**) were all isolated from cultures of *Phoma* sp. inhabiting *Sumbaviopsis albicans* and they showed cytotoxic activities.[74] (*R*)-Mellein (**91**) isolated from *Pezicula livida* residing in *Fagus sylvatica* indicated potent antimicrobial activities against *B. megaterium*, *E. coli*, *Ustilago violacea*, *Eurotium repens*, and *Cerospora fusca*.[75] (3*S*,4*S*)-3,8-Dihydroxy-6-methoxy-3,4,5-trimethylisochroman-1-one (**92**) and (3*R*,4*S*)-3,8-dihydroxy-3-hydroxymethyl-6-methoxy-4,5-dimethylisochroman-1-one (**93**) to reduce nitric oxide (NO) were obtained from *Phoma* sp. derived from *Artemisia princeps*.[76] Altenuene (**94**), 2-epialtenuene (**95**), alternariol (**96**), and alternariol 5-*O*-methyl ether (**97**) with cytotoxic activities were isolated from *Alternaria* sp. inhabiting *Polygonum senegalense*. In addition, alternariol and alternariol 5-*O*-methyl ether induced cytochrome P450 1A1 and caused apoptosis in murine heptatoma. Alternariol revealed to induce death of human colon carcinoma cells and inhibition of protein kinase and xanthine oxidase.[77-80] Graphislactone A (**98**) with strong antioxidant activity was isolated from *Cephalosporium* sp. in *Trachelospermum jasminoides* as well as *Microsphaeropsis olivacea* in *Pilgerodendron uviferum*.[81,82] Aurasperone A (**99**) and rubrofusarin B (**100**) were obtained from *Aspergillus niger* in *Cyndon dactylon* and they showed potent antimicrobial activities against some pathogens.[83] Aurasperone A was inhibitory on xanthine oxidase and rubrofusarin B was strongly cytotoxic to colon cancer cells.[83] Isofusidienols A-D (**101 - 104**) isolated from *Chalara* sp. inhabiting *Artemisia vulgaris* exhibited antimicrobial activities against *B. subtilis*, *S. aureus*, *E. coli*,

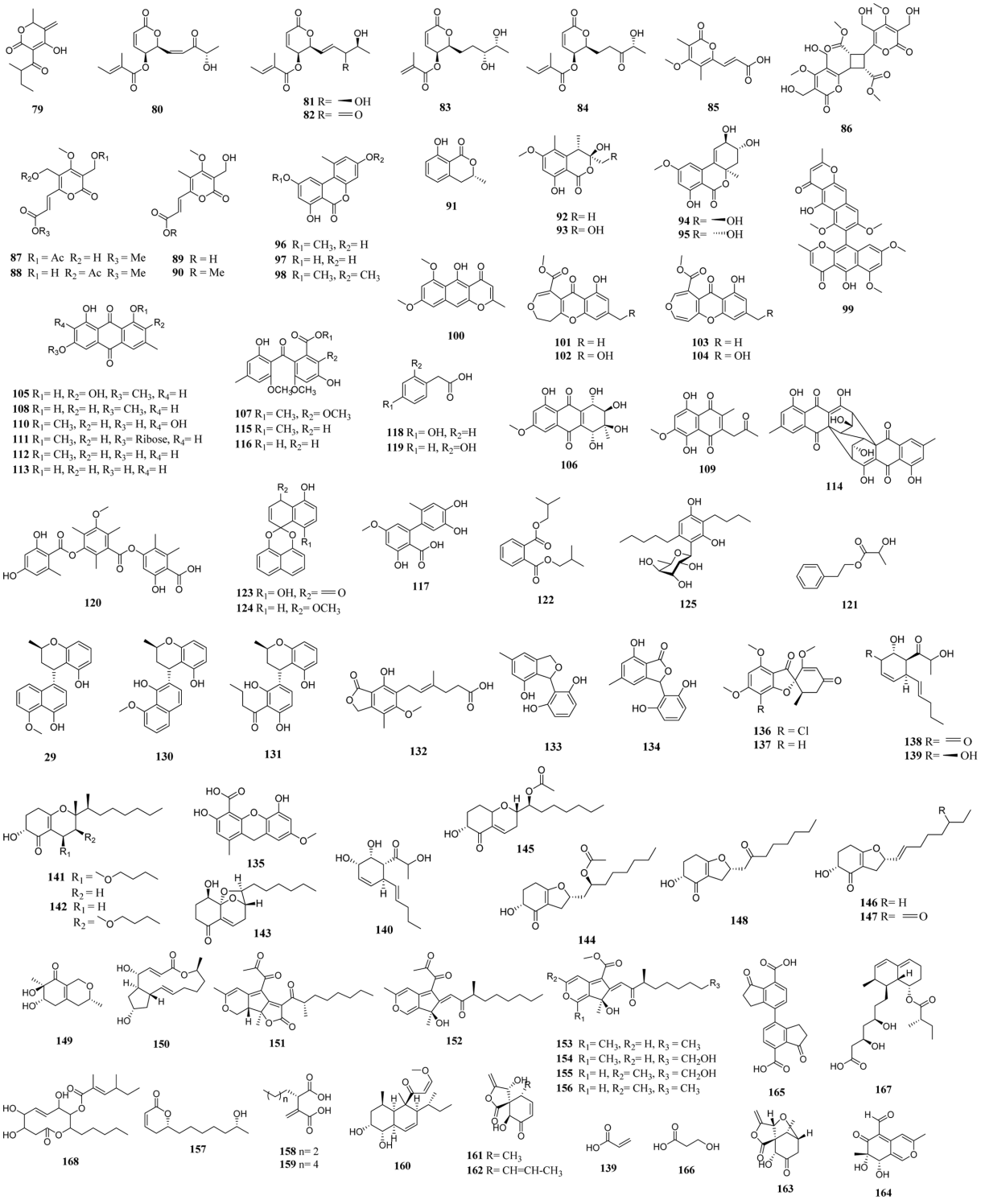

Fig. 6. Polyketides produced by endophytic fungi.

and *C. albicans*.[84]

Quinones including anthraquinones, secoanthraquinones, and bianthraquinones are another major polyketides produced by fungal endophytes as shown in Fig. 6. 3-*O*-Methylalaternin (**105**) and altersolanol A (**106**) from *Ampelomyces* sp. in *Urospermum picroides* showed strong antibacterial activities against *S. aureus*, *Staphylococcus epidermis*, *Enterococcus faecalis*.[85] Asperfumin (**107**) and

physcion (**108**) isolated from *A. niger* derived from *C. dactylon* showed antifungal activities against *C. albicans*.[24] Javanicin (**109**), isolated from *Chloridium* sp. inhabiting *Azadirachta indica*, exhibited antibacterial activities against *P. aeruginose* and *P. fluorescens*.[86] Evariquinone (**110**) isolated from cultures of *Colletotrichum* sp. residing in *Morus alba* showed potent protective activity against glutamate-induced neuronal cell death.[87] 1-*O*-Methyl-6-*O*-(α-D-ribofuranosyl)-emodin (**111**) and 1-*O*-methylemodin (**112**) isolated from cultures of *Gaeumannomyces* sp. derived from *P. communis* showed nitric oxide (NO) reduction activity. Moreover, 1-*O*-methylemodin revealed not only antifungal activity against *Phellinus tremulae* but also inhibition of secretion of IL-625, protein tyrosine phosphatase 1B, and acetylcholinesterase.[44,46,88-90] Emodin (**113**) with many biological activities, commonly isolated from the plant polygonaceae, was also isolated from cultures of *Mollisia* sp. derived from rook barks of *Ardisia cornudentata*.[46] Rugulosin (**114**) isolated from *Hormonema dematioides* residing in *Abies balsamea* caused liver cell necrosis as well as hepatocarcinogenesis to mice and rats.[91,92] Monomethylsulochrin (**115**) from *A. niger* derived from *C. dactylon* showed antimicrobial activities against *Helicobacter pylori*, *S. lutea*, *S. aureus*, and *C. albicans*.[39,40] Rhizoctonic acid (**116**), isolated from *Rhizoctonia* sp. inhabiting *C. dactylon*, exhibited anti-*Helicobacter pylori* activity.[39]

Many phenolic compounds have been reported from endophytic fungi as shown in Fig. 6. Altenusin (**117**), isolated from *Alternaria* sp. residing in *Trixis vauthieri*, exhibited inhibition of ribosomal protein synthesis as well as antifungal activity against *Paracoccidioides brasiliensis*.[93,94] 2-(4-Hydroxyphenyl)acetic acid (**118**) and 2-(2-hydroxyphenyl)acetic acid (**119**) isolated from *Colletotrichum gloeosporioides* derived from *Michelia champaca* showed antifungal activities against two plantpathogens, *Cladosporium cladosporioides* and *C. sphaerospermum,* that was comparable to that of the positive control nystatin.[26] Colletotric acid (**120**), isolated from *Colletotrichum gloeosporioides* of inhabiting *Artemisia mongolica*, exhibited antimicrobial activities against *B. subtilis*, *S. aureus*, *S. lutea*, and *H. sativum*.[95] Phenethyl 2-hydroxypropanoate (**121**) and phthalic acid diisobutyl ester (**122**), isolated from *C. gloeosporioides* residing in *A. sinensis*, showed growth inhibition of tumor cell lines MCF-7, NCI-H460, HepG-2, and SF-268.[51] Palmarumycin CP17 (**123**) and CP18 (**124**) obtained from *Edenia* sp. derived from *Petrea volubilis* showed not only antineoplastic activities but also growth inhibition of *Leishmania donovani*.[96] Resorcinol type compounds, stemphols C (**125**) and D (**126**), isolated from *Gaeumannomyces* sp. inhabiting *P. communis*, exhibited nitric oxide (NO) reduction activity.[28] Nodulosporins A and B (**127-128**) were obtained from *Nodulisporium* sp. derived from *Juniperus cedrus* and they showed antifungal activities against *Microbotryium violaceum*.[97] Nodulosporins D-F (**129-131**), isolated from *Nodulisporium* sp. inhabiting *Erica arborea*, exhibited antimicrobial activities against *B. megaterium* and *M. violaceum* as well as anti-algal activity against *Chlorella fusca*.[98,99] Mycophenolic acid (**132**), commonly known as fungal metabolite with strong immunosuppressant activity, was also isolated from an endophyte *Penicillium brevicompactum* residing in *Taxus brevifolia*.[100] Pestacin (**133**) and isopestacin (**134**) with potent antioxidant activity were isolated from *Pestalotiopsis microspora* derived from *Terminalia morobensis*.[101] Barceloneic acid C (**135**) isolated from *Phoma* sp. residing in *P. communis* exhibited antibacterial activities against *L. monocytogenes* and *Staphylococcus pseuditermedius*.[102] Griseofulvin (**136**) and dechlorogriseofulvin (**137**) used as antifungal agents were also isolated from an endophyte, *Xylaria* sp. derived from *Abies holophylla*.[103]

Polyketides not belonging to pyrones, quinones, and phenolics are also shown in Fig. 6. Colletotricone A (**138**), Nigrosporanenes A (**139**), and B (**140**), isolated from *P. sydowiana* of inhabiting *P. communis*, inhibited growth of MCF-7, NCI-H460, HepG-2, and SF-268 cancer cell lines.[51] Koningiopisins A-H (**141 - 148**) isolated from cultures of *Trichoderma koningiopsis* derived from *Panax notoginseng* showed antimicrobial activities against many pathogens such as *Bacillus anthracis*, *Enterococcus faecium*, *Staphylococcus aureus*, *S. simulans*, *S. epidermis*, *Streptococcus pneumoniae*, *Listeria monocytogenes*, *Shigella dysenteriae*, etc.[104] Miscellaneous polyketides have been isolated from endophytic fungi. Xylariphilone (**149**), isolated from *A. truncatum* of inhabiting *Z. caduciflora*, exhibited anti-inflammatory activity by reducing recreation of IL-6.[105] Brefeldin A (**150**), isolated from *Aspergillus clavatus* residing in *Tectona grandis* as well as *Paecilomyces* sp. in *Torreya mairei* exhibited not only anticancer activity against human lung cancer cell line Spc-A-1 but also antifungal activities against *A. niger*, *C. albicans*, and *Trichophyton rubrum*.[106] Sequoiatones A-F (**151 - 156**) were isolated from cultures of *Aspergillus parasiticus* derived from *Sequoia sempervirens*. **151** and **152** showed anticancer activity against breast cancer cell line while **153 - 156** exhibited brine shrimp lethality activity.[107,108] Gamagonolide A (**157**), isolated from *Epichloe typhina* inhabiting *Phleum pretense*, exhibited antifungal activity against *Cladosporium her-*

barum.[109] (2*S*)-Butylitaconic acid (**158**), (2*S*)-hexylitaconic acid (**159**), and eupenicinicol B (**160**) were isolated from cultures of *Eupenicillium* sp. harboring in *Xanthium sibiricum*. **158** and **159** showed profound antibacterial activity against *Acinetobacter* sp., supporting the notion that endophytes provide chemical defense to the host plants. **160** was highly active against clinically relevant *Staphylococcus aureus*.[110] Massarigenin D (**161**), arthropsolide A (**162**), and spiromassaritone (**163**) with antifungal activities against *Cryptococcus neoformans* and *T. rubrum* were obtained from *Massrison* sp. derived from *Rehmannia glutinosa*.[111] 7-Epiaustdiol (**164**), isolated from *Mycoleptodiscus* sp. harboring in *Tinospora crispa*, showed anti-oomycetic activities against *Aphanomyces cochlioides* and *Phytophthora sojaey*.[112] Nodulosporin C (**165**) with antifungal activity against *M. violaceum* was obtained from *Nodulisporium* sp. harboring in *J. cedrus*.[97] Brefeldine A (**150**), isolated from *Phoma medicaginis* inhabiting *Medicago sativa*, exhibited antibiotic activity as well as initiated apoptosis in cancer cells.[113] 3-Hydroxypropionic acid (**166**), isolated from *Phomopsis phaseoli* and *Melanconium betulinum* derived from *Betula pendula*, showed nematicidal activity against *Meloidogyne incognita* and *Caenorhabditis elegans*.[114] Mevinic acid (**167**) and phomol (**168**), isolated from *Phomopsis* sp. inhabiting Argentinean medicinal plant *Erythrina crista-galli*, exhibited anti-inflammatory activity in the mouse ear assay.[115]

Conclusion

In summary, 168 secondary metabolites isolated from endophytic fungi inhabiting medicinal plants have been discussed for their chemical structures and biological activities. Many of the endophytic fungi-derived compounds showed strong antibiotic activities and inhibitory activities against cancer cell growth. The characteristic bioactivities of the isolated secondary metabolites are expected to help understand the relationship between endophytic fungi and their medicinal plants. Further in-depth biological studies of the compounds isolated from cultures of endophytes are required to discover drug candidates from natural resources.

References

(1) Wink, M. Biochemistry of Plant Secondary Metabolism 2nd ed.; Wiley Online Library, Germany, **2010**, pp 1-17.
(2) Cragg, G. M.; Newman, D. J. *Biochim. Biophys. Acta* **2013**, *1830*, 3670-3695.
(3) Huang, S.; Zhang, J.; Tao, Z.; Lei, L.; Yu, Y.; Huang, L. *Plant Physiol. Biochem.* **2014**, *85*, 9-13.
(4) Tan, R. X.; Zou, W. X. *Nat. Prod. Rep.* **2001**, *18*, 448-459.
(5) Hardoim, P. R.; van Overbeek, L. S.; Berg, G.; Pirttila, A. M.; Compant, S.; Campisano, A.; Doring, M.; Sessitsch, A. *Microbiol. Mol. Biol. Rev.* **2015**, *79*, 293-320.
(6) de Siqueira, V. M.; Conti, R.; de Araújo, J. M.; Souza-Motta, C. M. *Symbiosis* **2011**, *53*, 89-95.
(7) Sun, X.; Guo, L. D. *Mycology* **2012**, *3*, 1-12.
(8) Dudeja, S. S.; Giri, R.; Saini, R.; Suneja-Madan, P.; Kothe, E. *J. Basic Microbiol.* **2012**, *52*, 248-260.
(9) Nisa, H.; Kamili, A. N.; Nawchoo, I. A.; Shafi, S.; Shameem, N.; Bandh, S. A. *Microb. Pathog.* **2015**, *82*, 50-59.
(10) Stierle, A.; Strobel, G.; Stierle, D. *Science* **1993**, *260*, 214-216.
(11) Zhao, J.; Zhou, L.; Wang, J.; Shan, T.; Zhong, L.; Liu, X.; Gao, X. *Curr. Res. Technol. Educ. Trop. Appl. Microbiol. Microb. Biotechnol.* **2010**, *1*, 567-576.
(12) Guo, B.; Li, H.; Zhang, L. *J. Yunnan Univ. (Natural Science)* **1998**, *20*, 214-215.
(13) Yang, X.; Guo, S.; Zhang, L.; Shao, H. *Nat. Prod. Res. Dev.* **2003**, *15*, 419-422.
(14) Kusari, S.; Zuhlke, S.; Spiteller, M. *J. Nat. Prod.* **2009**, *72*, 2-7.
(15) Zhnag, F. F.; Wang, M. Z.; Zheng, Y. X.; Liu, H. Y.; Zhang, X. Q.; Wu, S. S. *Mycobiology* **2015**, *84*, 701-709.
(16) Li, P.; Mou, Y.; Shan, T.; Xu, J.; Li, Y.; Lu, S.; Zhou, L. *Molecules* **2011**, *16*, 9003-9016.
(17) Kusari, S.; Lamshoft, M.; Zuhlke, S.; Spiteller, M. *J. Nat. Prod.* **2008**, *71*, 159-162.
(18) Kawada, M.; Inoue, H.; Ohba, S. I.; Masuda, T.; Momose, I.; Ikeda, D. *Int. J. Cancer* **2010**, *126*, 810-818.
(19) Strobel, G.; Daisy, B. *Microbiol. Mol. Biol. Rev.* **2003**, *67*, 491-502.
(20) Noble, H. M.; Langley, D.; Sidebottom, P. J.; Lane, S. J.; Fisher, P. J. *Mycol. Res.* **1991**, *95*, 1439-1440.
(21) Stierle, A. A.; Stierle, D. B. *Nat. Prod. Commun.* **2015**, *10*, 1671-1682.
(22) Shigeura, H. T.; Gordon, C. N. *Biochemistry* **1963**, *2*, 1132-1137.
(23) Ge, H. M.; Peng, H.; Guo, Z. K.; Cui, J. T.; Song, Y. C.; Tan, R. X. *Planta Med*. **2010**, *76*, 822-824.
(24) Liu, J. Y.; Song, Y. C.; Zhang, Z.; Wang, L.; Guo, Z. J.; Zou, W. X.; Tan, R. X. *J. Biotechnol*. **2004**, *114*, 279-287.
(25) Qin, J. C.; Zhang, Y. M.; Gao, J. M.; Bai, M. S.; Yang, S. X.; Laatsch, H.; Zhang, A. L. *Bioorg. Med. Chem. Lett*. **2009**, *19*, 1572-1574.
(26) Chapla, V. M.; Zeraik, M. L.; Leptokarydis, I. H.; Silva, G. H.; Bolzani, V. S.; Young, M. C. M.; Pfenning, L. H.; Araujo, A. R. *Molecules* **2014**, *19*, 19243-19252.
(27) Chithra, S.; Jasim, B.; Sachidanandan, P.; Jyothis, M.; Radhakrishnan, E. K. *Phytomedicine* **2014**, *21*, 534-540.
(28) Lee, C.; Kim, S.; Li, W.; Bang, S.; Lee, H.; Lee, H. J.; Noh, E. Y.; Park, J. E.; Bang, W. Y.; Shim, S. H. *J. Antibiot*. **2017**, *70*, 737-742.
(29) Li, J. Y.; Strobel, G.; Harper, J.; Lobkovsky, E.; Clardy. *J. Org. Lett.* **2000**, *2*, 767-770.
(30) Fábio, A.; Proenca, B.; Edson, R. F. *Biochem. Syst. Ecol*. **2005**, *33*, 257-268.
(31) Pongcharoen, W.; Rukachaisirikul, V.; Phongpaichit, S.; Rungjindamai, N.; Sakayaroj, J. *J. Nat. Prod*. **2006**, *69*, 856-858.
(32) Bang, S.; Song, J. H.; Lee, D.; Lee, C.; Kim, S.; Kang, K. S.; Lee, J. H.; Shim, S. H. *J. Agric. Food Chem.* **2019**, *67*, 1831-1838.
(33) Blanckenship, J. D.; Spiering, M. J.; Wilkinson, H. H.; Fannin, F. F.; Bush, L. P.; Schardl, C. L. *Phytochemistry* **2001**, *58*, 395-401.
(34) Wong, S. M.; Musza, L. L.; Kydd, G. C.; Kullnig, R.; Gillum, A. M.; Cooper, R. *J. Antibiot.* **1993**, *46*, 545-553.
(35) Bloch, P.; Tamm, C.; Bollinger, P.; Petcher, T. J.; Weber, H. P. *Helv. Chim. Acta* **1976**, *59*, 133-137.
(36) Horiuchi, M.; Tokuda, H.; Ohnishi, K.; Yamashita, M.; Nishino, H.;

Maoka, T. *Nat. Prod. Res.* **2006**, *20*, 161-166.
(37) Horn, W. S.; Simmonds, M. S. J.; Schwartz, R. E.; Blaney, W. M. *Tetrahedron* **1995**, *51*, 3969-3978.
(38) Chomcheon, P.; Wiyakrutta, S.; Sriubolmas, N.; Ngamrojanavanich, N.; Isarangkul, D.; Kittakoop, P. *J. Nat. Prod.* **2005**, *68*, 1103-1105.
(39) Ma, Y. M.; Li, Y.; Liu, J. Y.; Song, Y. C.; Tan, R. X. *Fitoterapia* **2004**, *75*, 451-456.
(40) Li, Y.; Song, Y. C.; Liu, J. Y.; Ma, Y. M.; Tan, R. X. *World J. Microbiol. Biotechnol*. **2005**, *21*, 553-558.
(41) Kongue Tatong, M. D.; Talontsi, F. M.; Abdel Rahim, H. M. D.; Islam, M. T.; Oswald, R. B.; Laatsch, H. *Tetrahedron Lett*. **2014**, *55*, 4057-4061.
(42) Li, W.; Sun, Y. N.; Lee, C.; Bang, S. H.; Kim, S.; Ma, J. Y.; Kim, Y. H.; Shim, S. H. *Arch. Pharm. Res.* **2017**, *40*, 152-158.
(43) Lu, H.; Zou, W. X.; Meng, J. C.; Hu, J.; Tan, R. X. *Plant Sci*. **2000**, *151*, 67-73.
(44) Li, Z.; Ma, N.; Zhao, P. J. *Nat. Prod. Res*. **2019**, *32*, 1794-1797.
(45) Zhang, W.; Draeger, S.; Schulz, B.; Krohn, K. *Nat. Prod. Commun*. **2009**, *4*, 1449-1454.
(46) Fan, N. W.; Chang, H. S.; Cheng, M. J.; Chan, H. Y.; Hsieh, S. Y.; Liu, T. W.; Chen, S. W.; Yuan, G. F.; Chen, I. S. *Chem. Nat. Compd.* **2016**, *52*, 585-590.
(47) Zheng, C. J.; Xu, L. L.; Li, Y. Y.; Han, T.; Zhang, Q. Y.; Ming, Q. L.; Rahman, K.; Qin, L. P. *Appl. Microbiol. Biotechnol*. **2013**, *97*, 7617-7625.
(48) Ratnaweera, P. B.; Williams, D. E.; Patrick, B. O.; de Silva, E. D.; Andersen, R. J. *Org. Lett.* **2015**, *17*, 2074-2077.
(49) Kong, F.; Wang, Y.; Liu, P.; Dong, T.; Zhu, W. *J. Nat. Prod.* **2014**, *77*, 132-137.
(50) Welch, T. R.; Williams, R. M. *Nat. Prod. Rep.* **2014**, *31*, 1376-1404.
(51) Xu, Y.; Espinosa-Artiles, P.; Liu, M. X.; Arnold, A. E.; Gunatilaka, A. A. L. *J. Nat. Prod*. **2013**, *76*, 2330-2336.
(52) Liu, H. X.; Tan, H. B.; Chen, Y. C.; Li, S. N.; Li, H. H.; Zhang, W. M. *Nat. Prod. Res.* **2018**, *32*, 2360-2365.
(53) Hiroyuki, K.; Satoshi, T.; Shun-ichi, T.; Yoshihara, T.; Sakamura, S.; Shimanuki, T.; Sato, T.; Tajimi, A. *Agric. Biol. Chem*. **1989**, *53*, 789-796.
(54) Silva, G. H.; Teles, H. L.; Zanardi, L. M.; Young, M. C. M.; Eberlin, M. N.; Hadad, R.; Pfenning, L. H.; Costa-Neto, C, M.; Castro-Gamboa, I.; de Silva Bolzani, V.; Araujo, A. R. *Phytochemistry* **2006**, *67*, 1964-1969.
(55) Xu, R.; Wang, M. Z.; Lu, C. H.; Zheng, Z. H.; Shen, Y. M. *Helv. Chim. Acta* **2009**, *92*, 1514-1519.
(56) Isaka, M.; Chinthanom, P.; Boonruangprapa, T.; Rungjindamai, N.; Pinruan, U. *J. Nat. Prod.* **2010**, *73*, 683-687.
57() Silva, G. H.; De Oliveira, C. M.; Teles, H. L.; Pauletti, P. M.; Castro-Gamboa, I.; Silva, D. H. S. Bolzani, V. S.; Young, M. C. M.; Costa-Neto, C. M.; Pfenning, L. H.; Berlinck, R. G. S.; Araujo, A. R. *Phytochem. Lett.* **2010**, *3*, 164-167.
(58) Hu, Z. Y.; Li, Y. Y.; Huang, Y. J.; Su, W. J.; Shen, Y. M. *Helv. Chim. Acta* **2008**, *91*, 46-52.
(59) Yuan, L.; Zhao, P. J.; Ma, J.; Lu, C. H.; Shen, Y. M. *Helv. Chim. Acta* **2009**, *92*, 1118-1125.
(60) Lee, J. C.; Lobkovsky, E.; Pliam, N. B.; Strobel, G.; Clardy, J. *J. Org. Chem.* **1995**, *60*, 7076-7077.
(61) dos Santos, R. M. G.; Rodrigues-Fo, E. *Z. Naturforsch. C. J. Biosci.* **2003**, *58*, 663-669.
(62) Kim, S.; Shin, D. S.; Lee, T.; Oh, K. B. *J. Nat. Prod.* **2004**, *67*, 448-450.
(63) Wijeratne, E. M. K.; Paranagama, P. A.; Marron, M. T.; Gunatilaka, M. K.; Arnold, A. E.; Gunatilaka, A. A. L. *J. Nat. Prod.* **2008**, *71*, 218-222.
(64) Serrano-Wu, M. H.; St. Laurent, D. R.; Mazzucco, C. E.; Stickle, T. M.; Barrett, J. F.; Vyas, D. M.; Balasubramanian, B. N. *Bioorg. Med. Chem. Lett.* **2002**, *12*, 943-946.
(65) Peláez, F.; Cabello, A.; Platas, G.; Díez, M. T.; González del Val, A.; Basilio, A.; Martán, I.; Vicente, F.; Bills, G. E.; Giacobbe, R. A.; Schwartz, R. E.; Onish, J. C.; Meinz, M. S.; Abruzzo, G. K.; Flattery, A. M.; Kong, L.; Kurtz, M. B. *Syst. Appl. Microbiol.* **2000**, *23*, 333-343.
(66) Onishi, J.; Meinz, M.; Thompson, J.; Curotto, J.; Dreikorn, S.; Rosenbach, M.; Douglas, C.; Abruzzo, G.; Flattery, A.; Kong, L.; Cabello, A.; Vicente, F.; Pelaez, F.; Diez, M. T.; Martin, I.; Bills, G.; Giacobbe, R.; Dombrowski, A.; Schwartz, R.; Morris, S.; Harris, G.; Tsipouras, A.; Wilson, K.; Kurtz, M. B. *Antimicrob. Agents Chemother*. **2000**, *44*, 368-377.
(67) Aly, A. H.; Debbab, A.; Proksch, P. *Appl. Microbiol. Biotechnol.* **2011**, *90*, 1829-1845.
(68) Kim, J. H.; Lee, C. H. *J. Microbiol. Biotechnol*. **2009**, *19*, 787-791.
(69) Yamaguchi, Y.; Manita, D.; Takeuchi, T.; Kuramochi, K.; Kuriyama, I.; Sugawara, F.; Yoshida, H.; Mizushina, Y. *Biosci. Biotechnol. Biochem*. **2010**, *74*, 793-801.
(70) Chen, L.; Chen, J.; Zheng, X.; Zheng, J.; Yu, X. *Nongyaoxue xuebao* **2007**, *9*, 143-148.
(71) Brady, S. F.; Clardy, J. *J. Nat. Prod.* **2000**, *63*, 1447-1448.
(72) Grove, J. F. *J. Chem. Soc. Perkin Trans.* **1985**, *1*, 865-869.
(73) Stierle, D. B.; Stierle, A. A.; Ganser, B. *J. Nat. Prod*. **1997**, *60*, 1207-1209.
(74) Sang, X. N.; Chen, S. F.; Tang, M. X.; Wang, H. F.; An, X.; Lu, X. J.; Zhao, D.; Wang, Y. B.; Bai, J.; Hua, H. M.; Chen, G.; Pei, Y. H. *Bioorg. Med. Chem. Lett*. **2017**, *27*, 3723-3725.
(75) Schulz, B.; Sucker, J.; Aust, H. J.; Krohn, K.; Ludewig, K.; Jones, P. G.; Doring, D. *Mycol. Res.* **1995**, *99*, 1007-1015.
(76) Kim, J. W.; Choi, H. G.; Song, J. H.; Kang, K. S.; Shim, S. H. *J. Antibiot.* **2019**, *72*, 174-177.
(77) Aly, A. H.; Edrada-Ebel, R.; Indriani, I. D.; Wray, V.; Muller, W. E. G.; Totzke, F.; Zirrgiebel, U.; Schachtele, C.; Kubbutat, M. H. G.; Lin, W. H.; Proksch, P.; Ebel, R. *J. Nat. Prod*. **2008**, *71*, 972-980.
(78) Gu, W. *World J. Microbiol. Biotechnol*. **2009**, *25*, 1677-1683.
(79) Bensassi, F.; Gallerne, C.; Sharaf El Dein, O.; Hajlaoui, M. R.; Bacha, H.; Lemaire, C. *Toxicol. In Vitro* **2012**, *26*, 915-923.
(80) Schreck, I.; Deigendesch, U.; Burkhardt, B.; Marko, D.; Weiss, C. *Arch. Toxicol*. **2012**, *86*, 625-632.
(81) Song, Y. C.; Huang, W. Y.; Sun, C.; Wang, F. W.; Tan, R. X. *Biol. Pharm. Bull.* **2005**, *28*, 506-509.
(82) Hormazabal, E.; Schmeda-Hirschmann, G.; Astudillo, L.; Rodriguez, J.; Theoduloz, C. *Z. Naturforsch C* **2005**, *60*, 11-21.
(83) Song, Y. C.; Li, H.; Ye, Y. H.; Shan, C. Y.; Yang, Y. M.; Tan, R. X. *FEMS Microbiol. Lett*. **2004**, *241*, 67-72.
(84) Lösgen, S.; Magull, J.; Schulz, B.; Draeger, S.; Zeeck, A. *European J. Org. Chem*. **2008**, *4*, 698-703.
(85) Aly, A. H.; Edrada-Ebel, R. A.; Wray, V.; Müller, W.; Kozytska, S.; Hentschel, U.; Proksch, P.; Ebel, R. Phytochemistry **2008**, *69*, 1716-1725.
(86) Kharwar, R. N.; Verma, V. C.; Kumar, A.; Gond, D. K.; Harper, J. K.; Hess, W. M.; Lobkovosky, E.; Ma, C.; Ren, Y. H.; Strobel, G. A. *Curr. Microbiol*. **2009**, *58*, 233-238.
(87) Song, J. H.; Bang, S.; Shin, M. S.; Lee, J.; Kang, K. S.; Shim, S. H. *J. Nat. Prod*. **2018**, *81*, 1411-1416.
(88) Gill, M.; Morgan, P. M. *Arkivoc* **2001**, *7*, 145-156.
(89) Na, M. K.; Jin, W. Y.; Min, B. S.; Ahn, J. S.; Bae, K. *Nat. Prod. Sci*. **2008**, *14*, 132-146.
(90) Yang, Y.; Yan, Y. M.; Wei, W.; Luo, J.; Zhang, L. S.; Zhou, X. J.; Wang, P. C.; Yang, Y. X.; Cheng, Y. X. *Bioorg. Med. Chem. Lett*. **2011**, *23*, 3905-3099.
(91) Ueno, Y.; Sato, N.; Ito, T.; Ueno, I.; Enomoto, M.; Tsunoda, H. *J. Toxicol. Sci.* **1980**, *5*, 295-302.

(92) Calhoun, L. A.; Findlay, J. A.; Miller, D. J.; Whitney, N. J. *Mycol. Res.* **1992**, *96*, 281-286.
(93) Cota, B. B.; Rosa, L. H.; Caligiorne, R. B.; Rabello, A. L.; Almeida Alves, T. M.; Rosa, C. A.; Zani, C. L. *FEMS Microbiol. Lett*. **2008**, *285*, 177-182.
(94) Johann, S.; Rosa, L. H.; Rosa, C. A.; Perez, P.; Cisalpino, P. S.; Zani, C. L.; Cota, B. B. *Rev. Iberoam. Micol.* **2012**, *29*, 205-209.
(95) Zou, W. X.; Meng, J. C.; Lu, H.; Chen, G. X.; Shi, G. X.; Zhang, T. Y.; Tan, R. X. *J. Nat. Prod*. **2000**, *63*, 1529-1530.
(96) Martínez-Luis, S.; Della-Togna, G.; Coley, P. D.; Kursar, T. A.; Gerwick, W. H.; Cubilla-Rios, L. *J. Nat. Prod*. **2008**, *71*, 2011-2014.
(97) Dai, J.; Krohn, K.; Flörke, U.; Draeger, S.; Schulz, B.; Kiss-Szikszai, A.; Antus, S.; Kurtan, T.; Van Ree, T. *Eur. J. Org. Chem*. **2006**, *15*, 3498-3506.
(98) Mousa, W. K.; Raizada, M. N. *Front. Microbiol*. **2013**, *4*, 65.
(99) Dai, J.; Krohn, K.; Draeger, S.; Schulz, B. *Eur. J. Org. Chem.* **2009**, *10*, 1564-1569.
(100) Gilliver, K. *Ann. Bot*. **1946**, *10*, 271-282.
(101) Strobel, G. A. Ford, E.; Worapong, J.; Harper, J. K.; Arif, A. M.; Grant, D. M.; Fung, P. C.; Ming Wah Chau, R. *Phytochemistry* **2002**, *60*, 179-183.
(102) Xia, X.; Kim, S.; Bang, S.; Lee, H. J.; Liu, C.; Park, C, I.; Shim, S. H. *J. Antibiot.* **2015**, *68*, 139-141.
(103) Park, J. H.; Choi, G. J.; Lee, H. B.; Kim, K. M.; Jung, H. S.; Lee, S. W.; Jang, K. S.; Cho, K. Y.; Kim, J. C. *J. Microbiol. Biotechnol.* **2005**, *15*, 112-117.
(104) Liu, K.; Yang, Y.; Miao, C. P.; Zheng, Y. K.; Chen, J. L.; Chen, Y. W.; Xu, L. H.; Guang, H. L.; Ding, Z. T.; Zhao, L. X. *Planta Med.* **2016**, *82*, 371-376.
(105) Li, W.; Lee, C.; Bang, S. H.; Ma, J. Y.; Kim, S.; Koh, Y. S.; Shim, S. H. *J. Nat. Prod*. **2017**, *80*, 205-209.
(106) Wang, J.; Huang, Y.; Fang, M.; Zhang, Y.; Zheng, Z.; Zhao, Y.; Su, W. *FEMS Immunol. Med. Microbiol*. **2002**, *34*, 51-57.
(107) Stierle, A. A.; Stierle, D. B.; Bugni, T. *J. Org. Chem*. **1999**, *64*, 5479-5484.
(108) Stierle, A. A.; Stierle, D. B.; Bugni, T. *J. Nat. Prod*. **2001**, *64*, 1350-1353.
(109) Koshino, H.; Yoshihara, T.; Okuno, M.; Sakamura, S.; Tajimi, A.; Shimanuki, T. *Biosci. Biotechnol. Biochem.* **1992**, *56*, 1096-1099.
(110) Li, G.; Kusari, S.; Lamshoft, M.; Schuffler, A.; Laatsch, H.; Spiteller, M. *J. Nat. Prod*. **2014**, *77*, 2335-2341.
(111) Sun, Z. L.; Zhang, M.; Zhang, J. F.; Feng, J. *Phytomedicine* **2011**, *18*, 859-862.
(112) Siriwach, R.; Kinoshita, H.; Kitani, S.; Igarashi, Y.; Pansuksan, K.; Panbangred, W.; Nihira, T. *J. Antibiot.* **2012**, *65*, 627-629.
(113) Weber, R. W.; Stenger, E.; Meffert, A.; Hahn, M. *Mycol. Res.* **2004**, *108*, 662-671.
(114) Schwarz, M.; Kopcke, B.; Weber, R. W.; Sterner, O.; Anke, H. *Phytochemistry* **2004**. *65*, 2239-2245.
(115) Weber, D.; Sterner, O.; Anke, T.; Gorzalczancy, S.; Martino, V.; Acevedo, C. *J. Antibiot.* **2004**. *57*, 559-563.

Received July 31, 2019
Revised September 11, 2019
Accepted September 18, 2019