


Review

Natural Products from Endophytic Fungi Associated with Rubiaceae Species

Jacqueline Santos Cruz ¹, Carla Amaral da Silva ^{2,*} and Lidilhone Hamerski ^{2,*} 

¹ Department of Chemistry, Military Institute of Engineering, Praça General Tibúrcio 80, Rio de Janeiro 22290-270, Brazil; jacquelinescruz@hotmail.com

² Walter Mors Institute of Research on Natural Products, Federal University of Rio de Janeiro, Rua Carlos Chagas Filho 373, Rio de Janeiro 21941-902, Brazil; carlota.amaral@gmail.com

* Correspondence: hamerski@ippn.ufrj.br; Tel.: +55-21-3938-6791

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Abstract: This review presents the chemical diversity and pharmacological properties of secondary metabolites produced by endophytic fungi associated with various genera of Rubiaceae. Several classes of natural products are described for these endophytes, although, this study highlights the importance of some metabolites, which are involved in antifungal, antibacterial, anti-protozoal activities; neurodegenerative diseases; cytotoxic activity; anti-inflammatory and antioxidant activity; and hyperglycemic control.

Keywords: Rubiaceae; endophytes; fungi; antibacterial; antifungal; neurodegenerative diseases; anti-inflammatory

1. Introduction

Natural products are small molecules from primary and secondary metabolites naturally synthesized by microorganisms, plants, or animals [1,2]. They are a continuing source of novel bioactive metabolites and have a significant impact on modern medicine [3,4]. Currently, more than 70% of antibacterial and anticancer compounds are natural products or their derivatives [5,6].

Fungi-derived natural products are considered one of the most relevant sources discovery and molecular diversity for new drugs. They are valuable source of biological metabolites that find wide-ranging applications as antibiotics, antifungal, immunosuppressants, antiparasitic and anticancer agents [7–12]. Among the microorganisms, endophytes have aroused interest in the last decades mainly for the discovery of important secondary metabolites identified from them.

The term endophyte refers to the microorganism that colonizes interior organs of plants, generally inhabiting their aerial parts such as stems and leaves, but that does not have pathogenic effects on its host [1,7,13–16]. Endophytes are ubiquitously found in every plant species examined to date. It is worth mentioning that, of the nearly 300,000 species on earth, each plant hosts one or more endophytes, and approximately 1 million of different species of microorganisms can be found [1,17]. In their symbiotic association, the host plant protects and feeds the endophyte, which in return produces bioactive metabolites to enhance the growth and competitiveness of the host and to protect it from herbivores and plant pathogens [7,9,18].

Endophytic fungi are known to produce a wide range of bioactive secondary metabolites, emphasizing chemical diversity, molecules originality and their biological activities [1,7,9,15–17,19–24]. Some studies suggest that up to 51% of bioactive metabolites obtained from endophytic fungi have unknown chemical structure, which highlights the huge biotechnological potential of this microbial group to the discovery of new drugs [21].

This review will focus on secondary metabolites synthesized by endophytic fungi isolated from Rubiaceae species, as well as the biological activities described in the literature for these compounds. The bibliographic research was carried out until March 2020.

2. Secondary Metabolites Produced by Endophytic Fungi from Rubiaceae

Rubiaceae is the fourth largest angiosperm family and comprises about 617 genera and 13,000 species of herbs, shrubs, and trees, found worldwide, especially in tropical and warm regions [25–27]. This family presents a vast diversity of chemical substances such as iridoids, anthraquinones, indole alkaloids, terpenoids, flavonoids, and alkaloids [28–32]. Diverse species of Rubiaceae have widespread use in folk medicine, and some of them showed anti-inflammatory, analgesic, antibacterial, mutagenic, antiviral, and antioxidant activities. Besides, an effect on vascular diseases and action on the central nervous system were observed [25,27,33,34].

The research on microorganisms associated with the Rubiaceae family, for biotechnological applications, led to the isolation of endophytic fungi [35–47] and the discovery of several bioactive metabolites [38,48–55]. The diversity of chemical structures observed for secondary metabolites synthesized by fungi isolated from Rubiaceae species showed a dynamic range of metabolites pathways used by these microorganisms.

Fungi secondary metabolites are categorized in chemical classes: polyketides [56–59], non-ribosomal peptides [57,59–62], ribosomal peptides [62–64], terpenes [65–67], and hybrid metabolites [68–74]. These chemical classes are synthesized by specialized class-defining (backbone) enzymes such as polyketides synthases (PKSs), non-ribosomal peptide synthetases (NRPSs), terpene cyclases (TCs), and dimethylallyl tryptophan synthases (DMATSs), respectively. The endophytes isolated from Rubiaceae showed the ability to produce these chemical classes (Figure 1). The set of enzymes needed for the production of a secondary metabolite is encoded by a gene cluster (BGC). Interestingly the genes that are essential for the synthesis of a primary metabolite are dispersed throughout the fungal genome, while the genes encoding the enzymatic activities for metabolic pathways to produce any secondary metabolite are arranged in continuous fashion. In the last decades, significant advances have been observed in the identification, understanding, and engineering of fungal biosynthetic gene clusters (BGCs) [75–84].

The endophytic fungi distribution and diversity in Rubiaceae have been reported since the 1950s [85–87], and studies performed with *Coffea arabica* stand out [88–92]. However, only in 1999 was the first study on the secondary metabolism of endophytic fungi isolated from Rubiaceae species published. In this work, Strobel related the occurrence of taxol (Figure 2), a potent anticancer drug, in the culture of the endophyte *Seimatoantlerium tepuiense* (Amphisphaeriaceae) isolated from *Maguireothamnus speciosus* [93]. The occurrence of taxol was described for other endophytes isolated from Rubiaceae species, *Botryodiplodia theobromae* (Botryosphaeriaceae) and *Aspergillus oryzae* (Trichomaceae), obtained from *Morinda citrifolia* and *Tarenna asiatica*, respectively [94–96]. The pharmacological properties of taxol, isolated from *Botryodiplodia theobromae*, were confirmed through the cytotoxicity assay [94].

The secondary metabolites study on microorganisms associated with Rubiaceae continued with *Palicourea marcgravi* St. Hil. It was popularly known as “erva de rato” and provided several endophytic fungi, including a *Xylaria* sp. (Xylariaceae) isolated from their leaves. The crude extract from *Xylaria* sp. showed a potential antifungal activity, and five compounds: 2-hexyl-3-methyl-butanodioic acid (1), cytochalasin D (2), 7-dechlorogriseofulvin (3), cytochalasin B (4) and griseofulvin (5) were obtained (Figure 3) [97].

Oliveira et al. (2009) explored endophytic fungi living in plants of the Brazilian flora; two *Penicillium* (Trichocomaceae) species from leaves of *Alibertia macrophylla* were isolated. *Penicillium* sp.1 was cultivated in corn and potato dextrose broth produced three different compounds: orcinol (6), cyclo-(L-Pro-L-Val) (7), uracil (8). The acetonitrile fraction from *Penicillium* sp.2 led to three dihydroisocoumarins: 4-hydroxymellein (9), 8-methyl-mellein (10) and 5-hydroxymellein (11) [98].

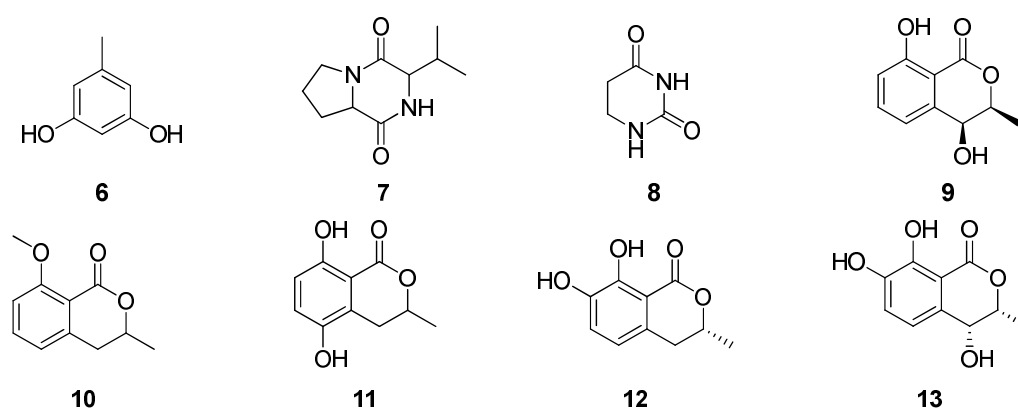


Figure 4. Compounds extracted from *Penicillium* species.

The continuing search for endophytes associated on *A. macrophylla* led to five new eremophilane sesquiterpenes: xylarenones C–G (**14–18**) isolated from solid cultures of *Camarops* sp. (Boliniaceae) [100,101]. This fungus was also able to produce two rearranged sesquiterpenes: 3,5,9-trihydroxy presilphiperfolane (**19**) and 4-deoxy-10-oxodihydrobotrydial (**20**); two branched polyketides: 4-((E)-pent-1-enyl)-3-((1'S,2'S)-1',2'-dihydroxybut-3-enyl)-5H-furan-2-one (**21**) and (2E,4R)-2,4-dimethylnon-2-enoic acid (**22**); seven phenolic derivatives: *p*-hydroxyphenyllactic acid (**23**), phenyllactic acid (**24**), *p*-hydroxybenzoic acid (**25**), *p*-hydroxybenzaldehyde (**26**), *n*-butyl-3,4-dihydroxybenzoate (**27**), *n*-hexyl-3,4-dihydroxybenzoate (**28**) and *n*-octyl-3,4-dihydroxybenzoate (**29**); and the known compound (2E,4S)-2,4-dimethyloct-2-enoic acid (**30**) (Figure 5) [102].

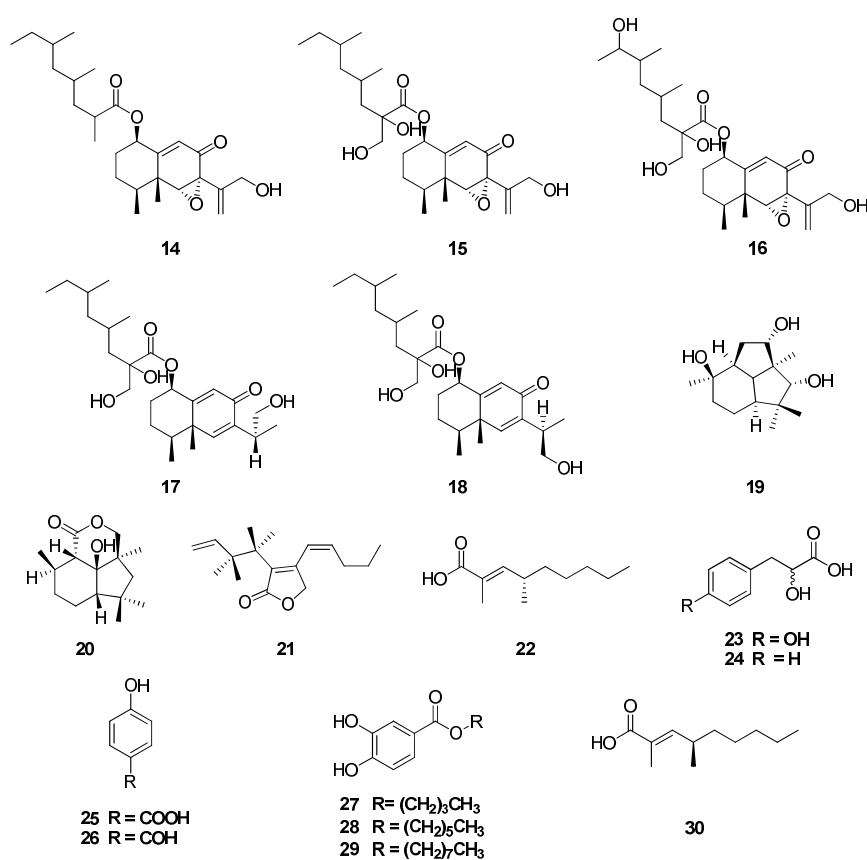


Figure 5. Compounds extracted from endophytes associated on *A. macrophylla*.

Extracts of solid cultures of *Sporormiella minimoides* (Sporormiaceae), isolated as an endophytic fungus from leaves *Hintonia latiflora* collected in Mexico, yielded five polyketides, 3,6-dimethoxy-8-methyl-1H,6Hbenzo[de]isochromene-1,9-dione (31), 3-hydroxy-1,6,10-trimethoxy-8-methyl-1H,3H-benzo[de]isochromen-9-one (32), 5-hydroxy-2,7-dimethoxy-8-methylnaphthoquinone (33), minimoidiones A (34) and B (35), along with four known compounds: corymbiferone (36), ziganein (37), brocaenol B (38) and preussochromone C (39) [103–105]. Two other compounds, 9S,11R(+)-ascosalitoxin (40) and vermelhotin (41), were also produced by endophytes from this plant [105,106]. The tridepsides, secondary metabolites produced by fungus *Chaetomium* sp. (Chaetomiaceae), also isolated from medicinal plant *H. latiflora*, were identified as thielavins A (42), J(43) and K (44) [107]. Two new compounds, pestalotin 4'-O-methyl- β -mannopyranoside (45) and 3S,4R-(+)-4-hydroxymellein (46), were isolated from an organic extract of *X. feejeensis*, which was isolated from this plant. In addition, the compounds (3S,4S)-4-hydroxymellein (9), (3S)-8-methylmellein (10), and the quinone derivatives 2-hydroxy-5-methoxy-3-methylcyclohexa-2,5-diene-1,4-dione (47), 4S,5S,6S-4-hydroxy-3-methoxy-5-methyl-5,6-epoxycyclohex-2-en-1-one (48), and 4R,5R-dihydroxy-3-methoxy-5-methylcyclohexen-2-en-1-one (49) were obtained (Figure 6) [108].

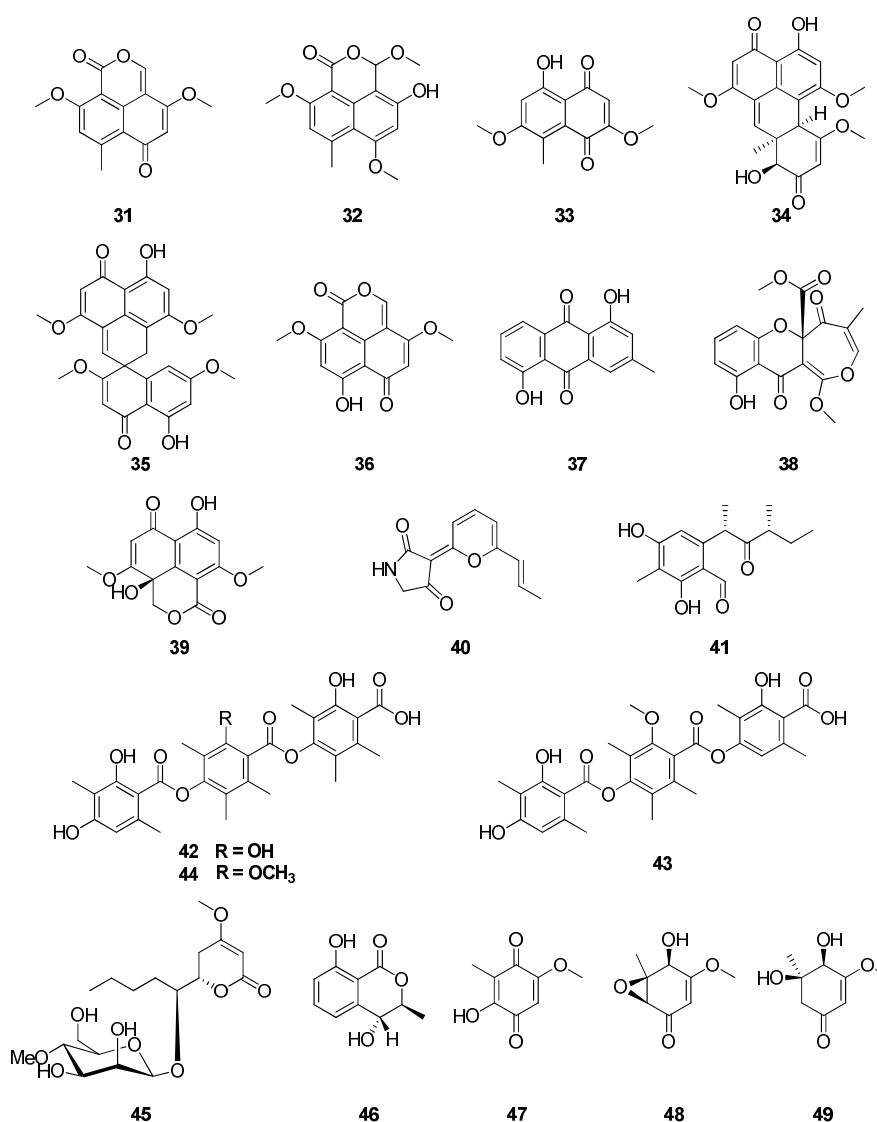


Figure 6. Compounds extracted from endophytic fungus *Sporormiella minimoides* obtained from *Hintonia latiflora*.

The ethyl acetate extract from *Cytospora rhizophorae* (Valsaceae), a fungus associated with *Morinda officinalis*, led to the isolation of three new compounds, named cytosporaphenones A–C (50–52), one new polyhydric benzophenone, and two new naphthopyrone derivatives, respectively. In addition to eight known compounds: 2-(2'S-hydroxypropyl)-5-methyl-7-hydroxychromone (53), 2-acetonil-7-hydroxy-5-methylchromone (54), 8-hydroxy-6-methylxanthone-1-carboxylic acid (55), regiolone (56), (3R,4R)-cis-4-hydroxy-5-methylmellein (57), scytalone (58), p-hydroxybenzoic acid (59) and 4-hydroxy-3-methoxybenzene-ethanol (60). Interestingly, all of them were identified from this strain for the first time, and these three new compounds (50–52) were the most highly oxygenated metabolites of their families discovered in nature [109].

The endophytic fungal strain *Alternaria* sp. (Pleosporaceae) isolated from medicinal plant *M. officinalis* produced two new metabolites, isobenzofuranone A (61) and indandione B (62), together with eleven known compounds (63–73): isosclerone (63), 2,4,8-trihydroxy-1-tetralone (64), 3,4-dihydro-3,4,8-trihydroxy-1[2H]-naphthalenone (65), 6-hydroxyisosclerone (66), cis-4-hydroxyscytalone (67), alternariol-4-methyl ether (68), 6-*epi*-stemphytriol (69), dihydroalterperyleneol (70), alterperyleneol (71), altertoxin II (72) and stemphyperyleneol (73). It is relevant emphasizing that indandione (62) showed a rarely occurring indanone skeleton in natural products (Figure 7) [110].

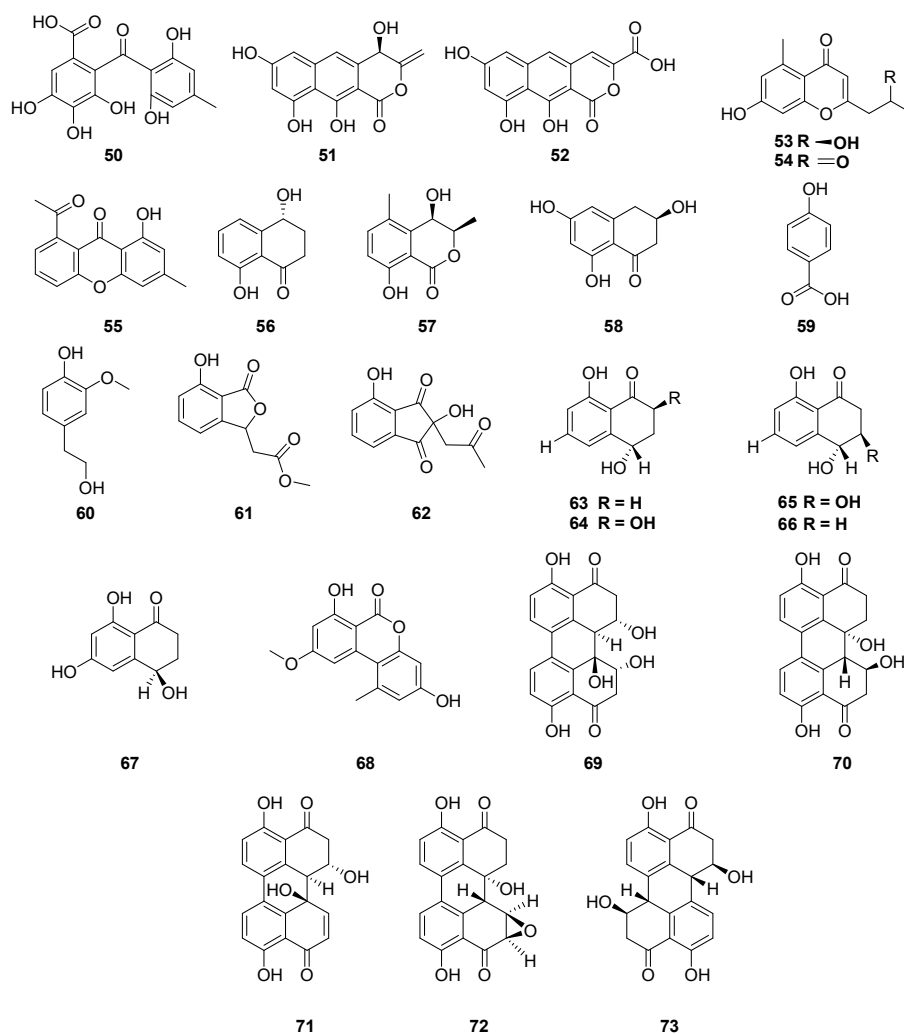


Figure 7. Compounds extracted from endophytic fungal strain *Alternaria* sp. isolated from medicinal plant *M. officinalis*.

The chemical investigation of the endophytic fungus *Trichoderma koningiopsis* (Hypocreaceae), also isolated from *M. officinalis* yielded three new diterpenes: koninginols A–C (74–76); two new sesquiterpenoids, 11-hydroxy-15-drimeneoic acid (77) and koninginol D (78); as well as twelve known metabolites identified as harziandione 2 (79), radianspene B (80), (S)-(-)-5-(hydroxymethyl)-2-(2',6',6'-trimethyltetrahydro-2H-pyran-2-yl)phenol (81), hamansol A (82), trichodermatide A (83), dihydropyran (84), ketodiol (85), 7-O-methylkoninginin D (86), (1S,6R,7S,10R)-10-hydroxy-4(5)-muurolen-3-one (87), 1R,3S,6S,7R,10S-7-isopropyl-4,10-dimethylbicyclo[4.4.0]dec-4-en-3,10-diol (88), 1R,3R,6S,7R,10S-7-isopropyl-4,10-dimethylbicyclo[4.4.0]dec-4-en-3,10-diol (89) and coprinol (90) [111]. Recently, six polyketides, 6-hydroxy-4-isopropyl-1,8-dimethylspiro[4.5]deca-1,8-dien-7-one (91), 2-hydroxy-2,5-dimethyl-7-oxo-5,7-dihydro-2H-furo[3,4-b]pyran-4-carboxylic acid (92), 3-ethyl-4-hydroxy-6-methyl-2H-pyran-2-one (93), harzialactone A (94), 3-hydroxy-5-(4-hydroxybenzyl)dihydrofuran-2(3H)-one (95), and 4-acetyl-3-hydroxy-6-methyl-pyran-2-one (96) were isolated from *T. spirale*, another endophytes from *M. officinalis* (Figure 8) [112].

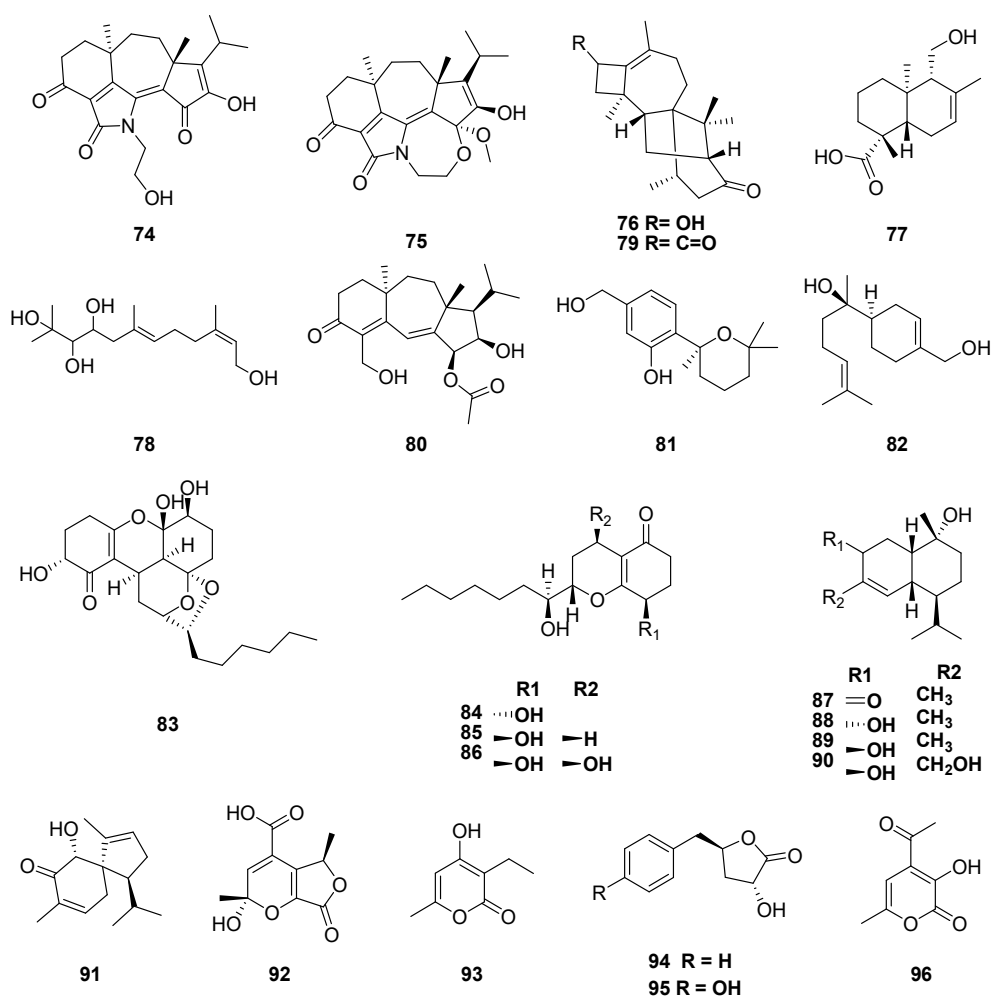


Figure 8. Compounds extracted from endophytic fungus *Trichoderma koningiopsis* (Hypocreaceae), also isolated from *M. officinalis*.

The endophytic fungi, *Cytospora rhizophorae* and *Diaporthe lithocarpus* (Diaporthaceae), were also obtained from *M. officinalis*. New metabolites isolated from *C. rhizophorae* included cytosporins A–D (97–100) meroterpenoids. These structures represent the first example of natural products that bear novel benzo[b][1,5]dioxocane framework embodying hemiterpene and benzophenone moieties [113]. Compounds 97–100 were evaluated for antimicrobial activities against *Escherichia coli* and *Staphylococcus aureus*. However, the compounds exhibited weak antibiotic activity with inhibition in concentrations

above $250 \mu\text{g mL}^{-1}$. The endophytic fungus, *D. lithocarpus*, yielded tenllone I (**101**), a new benzophenone derivative; two new eremophilane derivatives, lithocarins B (**102**) and C (**103**); a new monoterpene, lithocarin D (**104**); tenellone H (**105**); and phomopene (**106**) [114]. Studies of endophytic fungus of Nigerian medicinal plants led to isolation of multiforisin I (**107**) and 4-hydroxyphenylacetic acid (**108**) of *Neurospora discreta* (Sordariaceae) from leaves of *M. lucida* (Figure 9) [115].

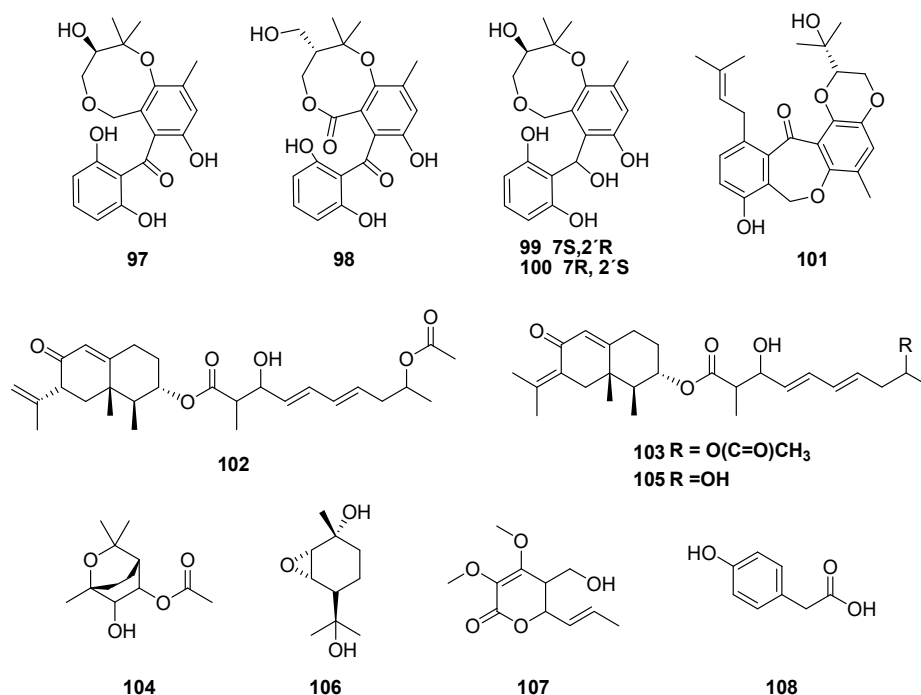


Figure 9. Compounds extracted from endophytic fungi, *Cytospora rhizophorae* and *Diaporthe lithocarpus* obtained from *M. officinalis*.

The curvularides A–E (**109–113**) are hybrid peptide–polyketides isolated from *Curvularia geniculata* (Pleosporaceae), an endophytic fungus obtained from the twigs of *Catunaregam tomentosa*. Their structures contain a 12-carbon atoms polyketide skeleton unit-linked, through an amide bond, with a derivative of L-isoleucine, a rare compound class [116]. The endophytic fungus *D. pseudomangiferae* retrieved from leaves of *Sabicea cinerea* species found along forest edges in the French Guiana, produces four metabolites: mycoepoxydiene (**114**) and altiloxin A (**115**), as well as enamidin (**116**) and eremofortin F (**117**) [117]. A filamentous fungus of the genus *Diaporthe* associated with the seeds of *Cinchona ledgeriana*, from West Java–Indonesia, produces cinchona alkaloids: quinine (**118**), quinidine (**119**), cinchonidine (**120**) and cinchonine (**121**), upon cultivation in a synthetic liquid medium [118–122]. Quinine (**118**), an antimalarial drug, has also been found in chloroform extracts of *Colletotrichum* spp. isolated from *C. calisaya* (Figure 10) [123].

Three new azaphilones with an unusual methylene bridge, named mycoleptones A, B, and C (**122–124**), were obtained from cultures of *Mycoleptodiscus indicus* (Magnaporthaceae), a fungus isolated from South American medicinal plant *Borreria verticillate* (Figure 10) [124]. Besides, other polyketides, austidiol (**125**), eugenitin (**126**), 6-methoxieugenin (**127**), and 9-hydroxyeugenin (**128**), were also produced (Figure 10) [124,125].

A fungus endophyte from *Uncaria rhynchophylla*, *C. gloeosporioides* (Glomerellaceae), produced four novel lactams in culture broth, colletotrilactam A–D (**129–132**); colletotrichine A (**133**) and B (**134**); and eleven more compounds: 2-isopropyl-5-methyl-2,4-cyclohexadien-1-ol (**135**), cis-4-hydroxymellein (**9**), 8-methyl-mellein (**10**), hederagonic acid (**136**), mellein (**137**) and blumenol A (**138**), aspergiketone (**139**), djalonenol (**140**), (4S)-(+)-ascochin (**141**), 12,13-dihydroxyfumitremorgin C (**142**) and fumitremorgin C (**143**) [124–126]. On the other hand, when grown in wheat bran medium, *C. gloeosporioides*

produced nine compounds: 4-epi-14-hydroxy-10, 23-dihydro-24, 25-dehydroaflavinine (**144**), 10, 23-dihydro-24,25-dehydro-21-oxoaflavinine (**145**), ergosterol (**146**), ergosterol peroxide (**147**), mellein (**137**), 4, 5-dihydroblumenol A (**148**), cyclo(L-leucyl-L-leucyl) (**149**), and brevianamide F (**150**). It was the first report of isolation of the compounds **144**, **145**, **148**, **149**, and **150** from the *Colletotrichum* genus (Figure 11) [127].

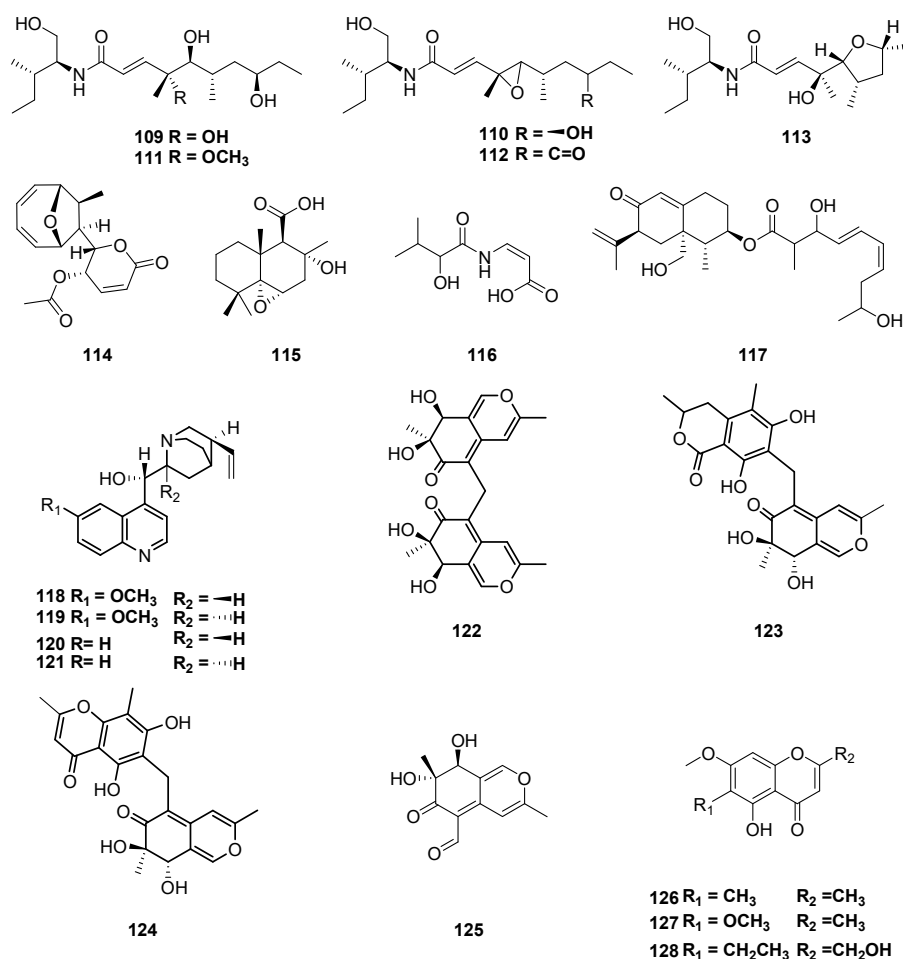


Figure 10. Compounds extracted from endophytic fungi, *Curvularia geniculata*, *D. pseudomangiferae*, *Diaporthe*, *Colletotrichum* spp and *Mycoleptodiscus indicus* obtained from *Catunaregam tomentosa*, *Sabicea cinerea*, *Cinchona ledgeriana*, *C. calisaya* and *Borreria verticillate*, respectively.

However, the chemical investigation of the *C. gloeosporioides* ethyl acetate extract, obtained from a solid culture, isolated from the leaves of *Sabicea cinerea*, led to the isolation of four new acoranes (**151–154**) and other seven known compounds: 5-hydroxymethyl-furan-2-carboxylic acid (**155**), 5-acetoxymethyl-furan-2-carboxylic acid (**156**), convolvulopyrone (**157**), p-hydroxybenzaldehyde (**158**), 4-hydroxyphenyl acetic acid (**159**), indole-3-carboxylic acid (**160**) and indole-3-carboxaldehyde (**161**) [128,129]. Recently, four cyclic tridepsipeptides, colletopeptides A–D (**162–165**), were isolated from *Colletotrichum* species from stems of *Rubia pandonantha* (Figure 12) [130].

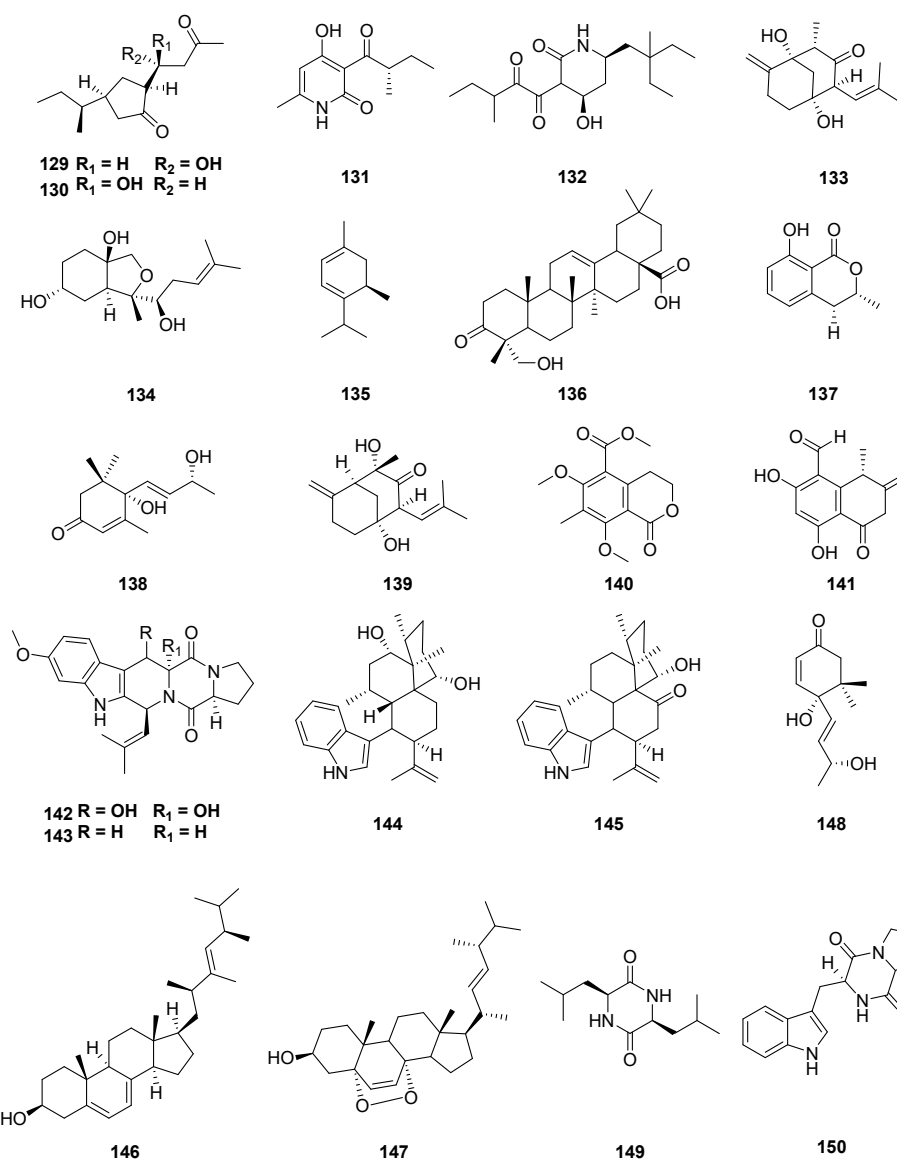


Figure 11. Compounds extracted from endophytic fungi, *C. gloeosporioides* obtained from *Uncaria rhynchophylla*.

Guignardia sp. (Botryosphaeriaceae) isolated from the leaves of the mangrove plant *Scyphiphora hydrophyllacea* Gaertn. F., produced six new meroterpenes, guignardones D–I (166–171); two known compounds, guignardones A (172) and B (173), and the fatty acid glucoside identified as (R)-3-hydroxyundecanoic acid methylester-3-O- α -L-rhamnopyranoside (174) [131–133]. Two other antibiotics, brefeldin A (175) and trichodermol (176), were isolated from endophytic fungus (code C22) from *S. hydrophyllacea* [134].

Analyzing the effect of the culture medium on the production of secondary metabolites by Panamanian endophytic fungi, an antiparasitic compound was obtained, cercosporin (177); and a new analog (178), isolated from endophytic fungus *Mycosphaerella* sp. (Mycosphaerellaceae), associated with the foliage of *Psychotria horizontalis* [135]. The structures of minor compounds in the extract were elucidated as 2-(2-butyl)-3-hydroxy-6-ethyl-6-methylcyclohex-2-ene-1,5-dione (179) and 3-(2-butyl)-6-ethyl-6-methyl-5-hydroxy-2-methoxy-cyclohex-2-eneone (180) (Figure 13) [136].

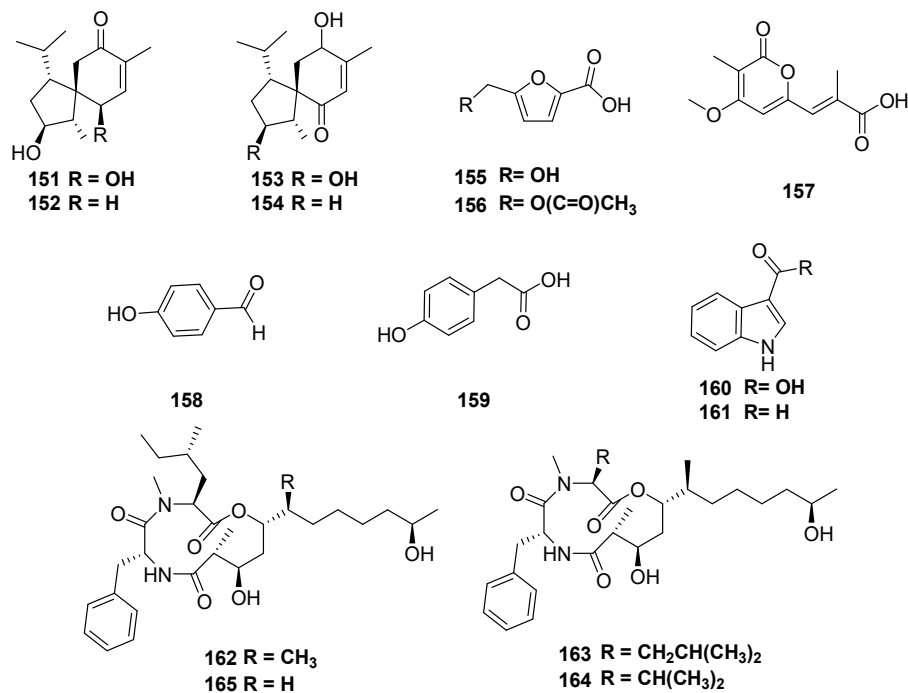


Figure 12. Compounds extracted from endophytic fungi, *Colletricium* sp. obtained from *Sabicea cinerea* and *Rubia pondantha*.

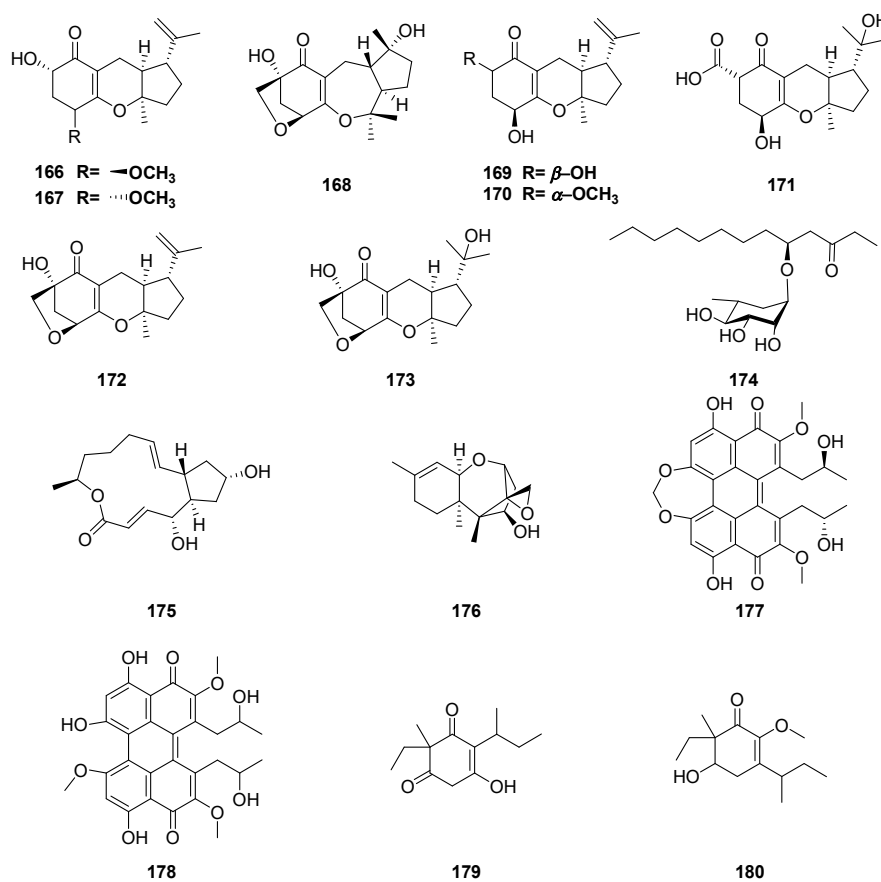


Figure 13. Compounds extracted from endophytic fungi, *Guignardia* sp and *Mycosphaerella* sp. obtained from *Scyphiphora hydrophyllacea* and *Psychotria horizontalis*, respectively.

In continuous studies on the chemistry of the endophytic fungus *P. griseoroseum* (Trichocomaceae), an endophyte isolated from fruits of *C. arabica*, produced dimethylated tetraketide diclavatol (**181**), clavatul (**182**) and two benzylated flavonoids (**183–184**) [137,138]. The studies also resulted in the identification of two known tetronic acids, viridicatic acid (**185**) and terrestric acid (**186**), found in ethyl acetate and n-butanol extract [138]. Mycophenolic acid (**187**), 5-hydroxy-7-methoxy-4-methylphtalide (**188**) and ochratoxin A (**189**) were produced by *P. crustosum* obtained from coffee seeds [139,140]. After adding halides in a broth culture, two bromoroquefortines, 11-bromoroquefortine D (**190**) and 11-bromo-17-hydroxybromoroquefortine C (**191**), were produced by *P. chrysogenum* from leaves of *C. arabica* (Figure 14) [141].

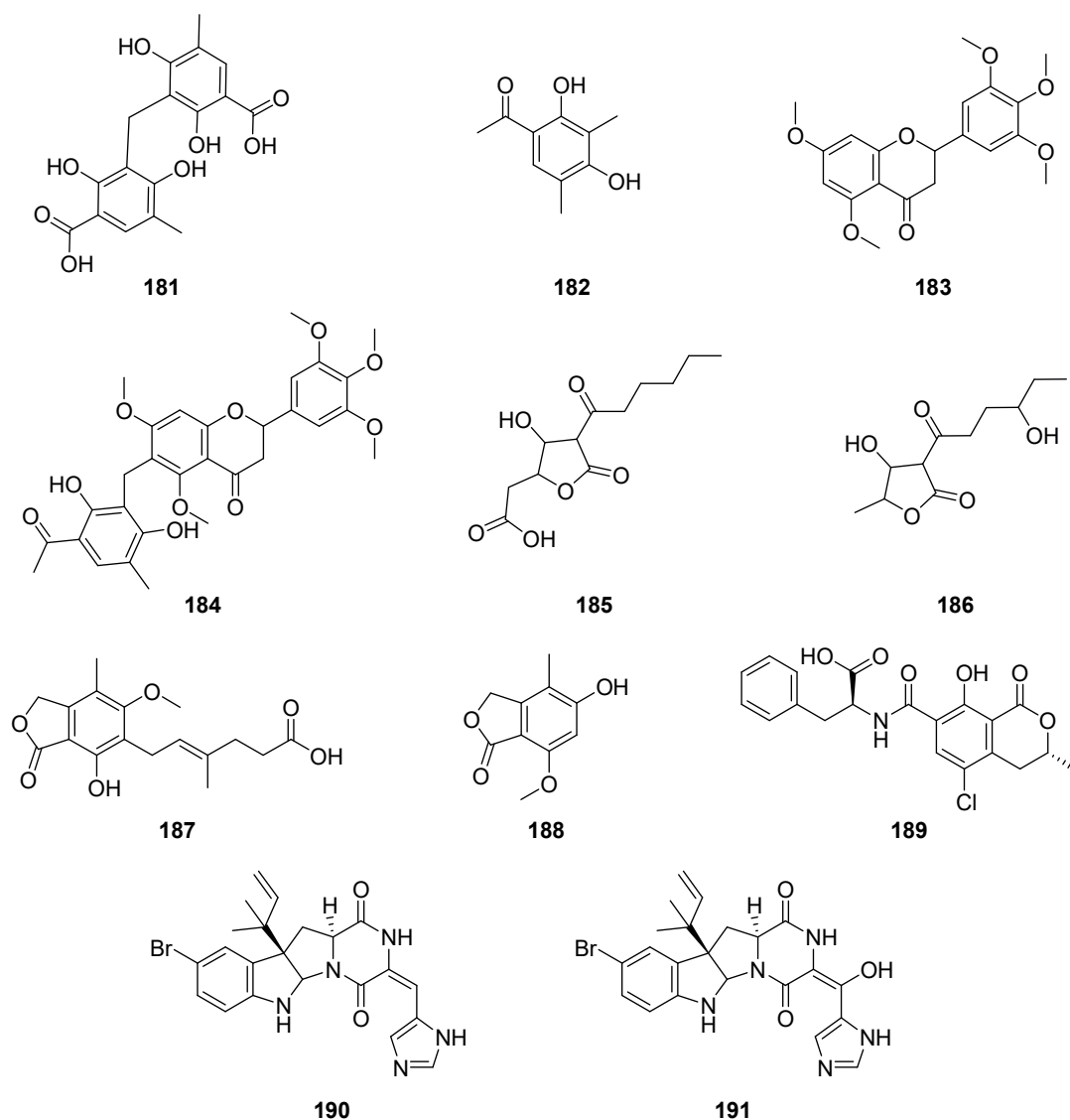


Figure 14. Compounds extracted from endophytic fungi, *P. griseoroseum*, *P. crustosum* and *P. chrysogenum* obtained from *C. arabica*.

An expedition to Yasuni National Park resulted in the isolation of endophytic *Stelliosphaera formicum* from *Duroia hirsuta*, an understory tree growing in Ecuador. Phylogenetic analysis of this organism describes it as a specimen of a new genus within the order Pleosporales. Besides this organism being an example of new taxonomic diversity, it also produced stelliophaerols A (**192**) and B (**193**), two new sesquiterpene-polyol conjugates 1 [142].

Chemical analyses of *Phomopsis* spp. (Valsaceae) isolated from tropical plants, including *C. arabica*, yielded alternariol (68), altenusin (194), altenuene (195), cytosporones C, O (196–197), and dothiorelones A–C (198–200) [143].

Recently, four secondary metabolites from *C. cupreum* associated with *Mussaenda luteola* were characterized as resorcinol (201), 6-(heptacosyl-18'Z enyl)-2-(18''hydroxyl-1'' enyl-19'' oxy)-3-hydroxybenzoquinone (202), (3 β -5 α -dihydroxy-6 β -phenylacetyloxy-ergosta-7, 22-diene) (203) and 2-dodecanol (204) (Figure 15) [144,145].

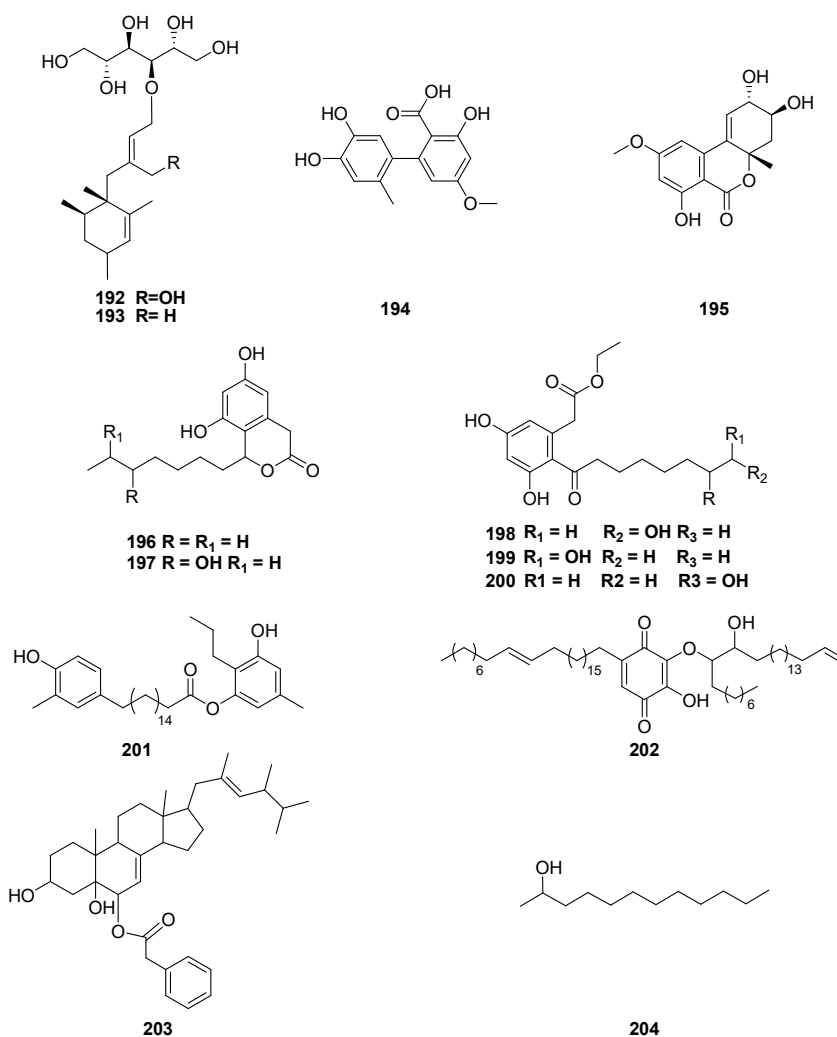


Figure 15. Compounds extracted from endophytic fungi, *Stelliosphaera formicum* *Phomopsis* spp and *C. cupreum* obtained from *Duroia hirsute*, *C. arabica* and *Mussaenda luteola*, respectively.

3. Biological Activities

Endophyte fungi are capable of synthesizing bioactive compounds, including alkaloids, terpenoids, flavonoids and steroids. Hitherto, most of the secondary metabolites from endophytes are anticancer agents, antibiotics, biological control agents, and other bioactive compounds determined by their different functional roles. In this review, we highlight mainly bioactive natural products endophytically synthesized by endophytic fungi associated with various genera of Rubiaceae (Table 1).

Table 1. Compounds produced by endophytic fungi associated with various genera of Rubiaceae and their respectively biological activities.

Classification	Compound	Endophytic	Species	Biological Activities	Reference
alkaloid	cytochalasin D (2)	<i>Xylaria</i> sp.	<i>Palicourea marcgravii</i>	antifungal	[97]
alkaloid	quinine (118)	<i>Colletotrichum</i> spp.	<i>Cinchona ledgeriana</i>	antiprotozoal	[120,121,146]
alkaloid	brevianamide F (150)	<i>Colletotrichum gloeosporioides</i>	<i>Uncaria rhynchophylla</i>	cytotoxic	[127]
alkaloid	11-bromoroquefortine (190)	<i>Penicillium chrysogenum</i>	<i>Coffea arabica</i>	antibacterial, antiprotozoal, cytotoxic	[141]
coumarin	4-hydroxy-mellein (9)	<i>Penicillium</i> sp.	<i>Alibertia macrophylla</i>	antifungal, acetylcholinesterase inhibitor, anti-hyperglycemic	[98]
coumarin	8-methyl-mellein (10)	<i>Penicillium</i> sp.	<i>Alibertia macrophylla</i>	Antifungal	[98]
coumarin	(R)-7-hydroxymellein (12)	<i>Penicillium</i> sp.	<i>Alibertia macrophylla</i>	antifungal, acetylcholinesterase inhibitor	[99]
coumarin	(3R,4R)-4,7-dihydroxymellein (13)	<i>Penicillium</i> sp.	<i>Alibertia macrophylla</i>	antifungal, acetylcholinesterase inhibitor	[99]
coumarin	3S,4R-(+)-4-hydroxymellein (46)	<i>Xylaria feejeensis</i>	<i>Hintonia latiflora</i>	anti-hyperglycemic	[108]
coumarin	mellein (137)	<i>Colletotrichum gloeosporioides</i>	<i>Uncaria rhynchophylla</i>	monoamine oxidase inhibitor	[127]
diketopiperazine	cyclo-(L-Pro-L-Val) (7)	<i>Penicillium</i> sp.	<i>Alibertia macrophylla</i>	acetylcholinesterase inhibitor	[98]
diketopiperazine	cyclo(L-Leu-L-Leu) (149)	<i>Colletotrichum gloeosporioides</i>	<i>Uncaria rhynchophylla</i>	cytotoxic	[127]
diterpene	koninginol A (74)	<i>Trichoderma koningiopsis</i>	<i>Morinda officinalis</i>	antifungal	[111]
diterpene	koninginol B (75)	<i>Trichoderma koningiopsis</i>	<i>Morinda officinalis</i>	antifungal, cytotoxic	[111]
fatty acid	(R)-3-hydroxyundecanoic acid methylester-3-O- α -L-rhamnopyranoside (174)	<i>Guignardia</i> sp.	<i>Scyphiphora hydrophyllacea</i>	antibacterial	[133]
meroterpene	guignardone I (171)	<i>Guignardia</i> sp.	<i>Scyphiphora hydrophyllacea</i>	antibacterial	[132]
meroterpene	guignardone B (173)	<i>Guignardia</i> sp.	<i>Scyphiphora hydrophyllacea</i>	antibacterial	[132]
phenolic compound	orcinol (6)	<i>Penicillium</i> sp.	<i>Alibertia macrophylla</i>	antifungal	[98]
phenolic compound	thielavins A (42)	<i>Chaetomium</i> sp.	<i>Hintonia latiflora</i>	anti-hyperglycemic	[107]
phenolic compound	thielavins J (43)	<i>Chaetomium</i> sp.	<i>Hintonia latiflora</i>	anti-hyperglycemic	[107]
phenolic compound	thielavins K (44)	<i>Chaetomium</i> sp.	<i>Hintonia latiflora</i>	anti-hyperglycemic	[107]
phenolic compound	cytosporaphenone A (50)	<i>Cytospora rhizophorae</i>	<i>Morinda officinalis</i>	cytotoxic	[109]
phenolic compound	resorcinol (201)	<i>Chaetomium cupreum</i>	<i>Mussaenda luteola</i>	antibacterial	[145]
polyketide	2-hexyl-3-methyl-butanodioic acid (1)	<i>Xylaria</i> sp.	<i>Palicourea marcgravii</i>	antifungal	[97]
polyketide	(2E,4R)-2,4-dimethylnon-2-enoic acid (22)	<i>Camarops</i> sp.	<i>Alibertia macrophylla</i>	acetylcholinesterase inhibitor	[102]
polyketide	(2E,4S)-2,4-dimethyloct-2-enoic acid (30)	<i>Camarops</i> sp.	<i>Alibertia macrophylla</i>	acetylcholinesterase inhibitor	[102]
polyketide	5-hydroxy-2,7-dimethoxy-8-methylnaphthoquinone (33)	<i>Sporormiella minimoides</i>	<i>Hintonia latiflora</i>	human calmodulin inhibitor	[103]
polyketide	minimoidione (34)	<i>Sporormiella minimoides</i>	<i>Hintonia latiflora</i>	anti-hyperglycemic	[104]
polyketide	vermelhotin (41)	<i>Sporormiella minimoides</i>	<i>Hintonia latiflora</i>	human calmodulin inhibitor	[106]
polyketide	2,4,8-trihydroxy-1-tetralone (64)	<i>Alternaria</i> sp.	<i>Morinda officinalis</i>	anti-hyperglycemic	[110]
polyketide	3,4-dihydro-3,4,8-trihydroxy-1[2H]-naphthalenone (65)	<i>Alternaria</i> sp.	<i>Morinda officinalis</i>	anti-hyperglycemic	[110]
polyketide	6-hydroxy-4-isopropyl-1,8-dimethylspiro[4.5]deca-1,8-dien-7-one (91)	<i>Trichoderma spirale</i>	<i>Morinda officinalis</i>	cytotoxic	[112]

Table 1. Cont.

Classification	Compound	Endophytic	Species	Biological Activities	Reference
polyketide	2-hydroxy-2,5-dimethyl-7-oxo-5,7-dihydro-2H-furo[3,4-b]pyran-4-carboxylic acid (92)	<i>Trichoderma spirale</i>	<i>Morinda officinalis</i>	cytotoxic	[112]
polyketide	3-ethyl-4-hydroxy-6-methyl-2H-pyran-2-one (93)	<i>Trichoderma spirale</i>	<i>Morinda officinalis</i>	cytotoxic	[112]
polyketide	harzialactone A (94)	<i>Trichoderma spirale</i>	<i>Morinda officinalis</i>	cytotoxic	[112]
polyketide	3-hydroxy-5-(4-hydroxybenzyl)dihydrofuran-2(3H)-one (95)	<i>Trichoderma spirale</i>	<i>Morinda officinalis</i>	cytotoxic	[112]
polyketide	4-acetyl-3-hydroxy-6-methyl-pyran-2-one (96)	<i>Trichoderma spirale</i>	<i>Morinda officinalis</i>	cytotoxic	[112]
polyketide	multiforisin I (107)	<i>Neurospora discrete</i>	<i>Morinda lucida</i>	cytotoxic	[115]
polyketide	curvularide B (110)	<i>Curvularia geniculata</i>	<i>Catunaregam tomentosa</i>	antifungal	[116]
polyketide	mycoepoxydiene (114)	<i>Diaporthe pseudomangiferae</i>	<i>Cinchona ledgeriana</i>	cytotoxic	[117]
polyketide	mycoleptones A (122)	<i>Mycoleptodiscus indicus</i>	<i>Borreria verticillata</i>	antiprotozoal, cytotoxic	[146]
polyketide	mycoleptones B (123)	<i>Mycoleptodiscus indicus</i>	<i>Borreria verticillata</i>	antiprotozoal	[130]
polyketide	austidiol (125)	<i>Mycoleptodiscus indicus</i>	<i>Borreria verticillata</i>	antiprotozoal	[130]
polyketide	colletopeptide A (162)	<i>Colletotrichum</i> sp.	<i>Rubia pondantha</i>	anti-inflammatory, antioxidant	[130]
polyketide	colletopeptide B (163)	<i>Colletotrichum</i> sp.	<i>Rubia pondantha</i>	anti-inflammatory, antioxidant	[130]
polyketide	colletopeptide C (164)	<i>Colletotrichum</i> sp.	<i>Rubia pondantha</i>	anti-inflammatory, antioxidant	[130]
polyketide	colletopeptide D (165)	<i>Colletotrichum</i> sp.	<i>Rubia pondantha</i>	anti-inflammatory, antioxidant	[130]
quinone	6- <i>epi</i> -stemphytriol (69)	<i>Alternaria</i> sp.	<i>Morinda officinalis</i>	anti-hyperglycemic	[110]
quinone	dihydroalterperyleneol (70)	<i>Alternaria</i> sp.	<i>Morinda officinalis</i>	anti-hyperglycemic, cytotoxic	[110]
quinone	alterperyleneol (71)	<i>Alternaria</i> sp.	<i>Morinda officinalis</i>	cytotoxic	[110]
quinone	altertoxin II (72)	<i>Alternaria</i> sp.	<i>Morinda officinalis</i>	anti-hyperglycemic	[110]
quinone	stemphyperyleneol (73)	<i>Alternaria</i> sp.	<i>Morinda officinalis</i>	antifungal, anti-hyperglycemic	[110]
quinone	cerosporin (177)	<i>Mycosphaerella</i> sp.	<i>Psychotria horizontalis</i>	antiprotozoal, cytotoxic	[127,128,135]
quinone	6-(heptacosyl-18'-Zenyl)-2-(18''hydroxyl-1''enyl-19''oxy)-3-hydroxybenzoquinone (202)	<i>Chaetomium cupreum</i>	<i>Mussaenda luteola</i>	antibacterial, cytotoxic	[145]
sesquiterpene	xylarenones G (18)	<i>Camarops</i> sp.	<i>Alibertia macrophylla</i>	anti-inflammatory	[100]
sesquiterpene	1R,3S,6S,7R,10S-7-isopropyl-4,10-dimethylbicyclo[4.4.0]dec-4-en-3,10-diol (88)	<i>Trichoderma koningiopsis</i>	<i>Morinda officinalis</i>	cytotoxic	[111]
sesquiterpene	1R,3R,6S,7R,10S-7-isopropyl-4,10-dimethylbicyclo[4.4.0]dec-4-en-3,10-diol (89)	<i>Trichoderma koningiopsis</i>	<i>Morinda officinalis</i>	cytotoxic	[111]
sesquiterpene	lithocarin B (102)	<i>Diaporthe lithocarpus</i>	<i>Morinda officinalis</i>	cytotoxic	[114]
sesquiterpene	lithocarin C (103)	<i>Diaporthe lithocarpus</i>	<i>Morinda officinalis</i>	cytotoxic	[114]
sesquiterpene	tenellone H (105)	<i>Diaporthe lithocarpus</i>	<i>Morinda officinalis</i>	cytotoxic	[114]
sesquiterpene	eremofortin F (117)	<i>Diaporthe pseudomangiferae</i>	<i>Cinchona ledgeriana</i>	cytotoxic	[117]
sesquiterpene	colletotrichine A (133)	<i>Colletotrichum gloeosporioides</i>	<i>Uncaria rhynchophylla</i>	acetylcholinesterase inhibitor	[125]
sesquiterpene	colletotrichine B (134)	<i>Colletotrichum gloeosporioides</i>	<i>Uncaria rhynchophylla</i>	acetylcholinesterase inhibitor	[126]
sesquiterpene	stelliosphaerols A (192)	<i>Stelliosphaera formicum</i>	<i>Duroia hirsuta</i>	antibacterial	[142]
sesquiterpene	stelliosphaerols B (193)	<i>Stelliosphaera formicum</i>	<i>Duroia hirsuta</i>	antibacterial	[142]
steroid	(3 β -5 α -dihydroxy-6 β -phenylacetyloxy-ergosta-7, 22-diene) (203)	<i>Chaetomium cupreum</i>	<i>Mussaenda luteola</i>	antibacterial, cytotoxic	[145]

3.1. Antifungal and Antibacterial Activity

Thin layer chromatography (TLC) bioautography indicated that compounds **1** and **2** (isolated from *Xylaria* sp.) and compounds **6**, **9**, **10**, **12**, and **13** (isolated from *Penicillium* sp.) display activity against *Cladosporium cladosporioides* and *C. sphaerospermum*. The most active compounds, orcinol (**6**), 4-hydroxymellein (**9**), (R)-7-hydroxymellein (**12**) and (3R,4R)-4,7-dihydroxymellein (**13**) showed a potent effect exhibiting a detection limit of 5.0 and 10.0 $\mu\text{g mL}^{-1}$ against *C. cladosporioides* and *C. sphaerospermum*, respectively [97–99]. In a disk diffusion assay, curvularide B (**110**) exhibited activity against *Candida albicans* with an inhibition zone diameter of 12.1 mm; it also showed synergistic effect with a fluconazole drug [116].

Crude extracts of *S. formicum* from *D. hirsuta* showed specific activity against *Staphylococcus aureus*. Stellosphaerols A (**192**) and B (**193**) were subsequently isolated by bioassay-guided isolation as causative agents of this activity. Following it, the growth inhibition assays revealed minimum inhibitory concentration (MIC) values for stellosphaerols A and B of approximately 250 $\mu\text{g mL}^{-1}$ [142]. On the other hand, the meroterpene guignardone I (**171**), guignardone B (**173**) and the fatty acid glucoside (**174**) produced by the endophytic fungal from *S. hydrophyllacea* showed modest inhibitory effects on *S. aureus* and methicillin-resistant *S. aureus* (MRSA) [132,133].

Two new diterpenes, koninginols A (**74**) and B (**75**), isolated from the endophytic fungus *T. koningiopsis* derived from *M. officinalis*, exhibited significant antibacterial activity against *B. subtilis* with MIC values of 10 and 2 $\mu\text{g mL}^{-1}$, respectively [111]. Moreover, the alkaloid 11-bromoroquefortine D (**190**) was also able to inhibit this bacterium at a concentration of 15 mM [141]. Metabolites **201**, **202** and **203** isolated from *C. cupreum* showed anti-mycobacterial activity against *Mycobacterium tuberculosis*, with MIC values of 6.3, 6.25 and 25 $\mu\text{g mL}^{-1}$ [145].

3.2. Neurodegenerative Diseases

Acetylcholinesterase (AChE) and monoamine oxidase (MAO) are enzymatic targets for the search of new drugs for the treatment of neurodegenerative diseases [147–150]. Diketopiperazine **7** and the dihydroisocoumarins **12**, **13**, and **9**, isolated from *Penicillium* sp. associated with *A. macrophylla*, exhibited AChE inhibitory activity and showed a detection limit of 10.0 μg (**7**, **12**, **13**) and 30.0 μg (**9**), respectively [98,99]. On the other hand, xylarenone C (**14**) isolated from *Camarops* sp., had a minimum AChE inhibitory concentration of 6.25 μg , while the others compound (**15**, **22**, and **30**) from *Camarops* sp., showed weak acetylcholinesterase (AChE) inhibitory activity [101]. Recently, the sesquiterpenoids colletotrichines A (**133**) and B (**134**) produced by *C. gloeosporioides* inhibited AChE activity with the half-maximal inhibitory concentration IC_{50} values of 28.0 and 38.0 $\mu\text{g mL}^{-1}$, respectively [125,126].

Monoamine oxidase (MAO) is an enzyme that catalyzes the oxidative deamination of biogenic amines neurotransmitters. Besides, MAO plays an essential role in the central nervous system and peripheral organs [151,152]. Compound mellein (**137**), produced by *C. gloeosporioides*, showed potent MAO inhibitory activity with an IC_{50} value of $8.93 \pm 0.34 \mu\text{g mL}^{-1}$, while the standard, iproniazid, was $1.80 \pm 0.5 \mu\text{g mL}^{-1}$ [124].

3.3. Cytotoxic Activity

The eremophilane sesquiterpenes xylarenone C (**14**) and xylarenone D (**15**), isolated from *Camarops* sp., exhibited cytotoxic activity against human tumor cell lines, such as leukemia (HL-60), melanoma (MDA/MB-435), colon (HCT-8), and glioblastoma (SF-295). The antiproliferative effect was evaluated following 72h of treatment, and the compounds **14** and **15** were more active against MDA/MB-435 ($\text{IC}_{50} = 2.4 \mu\text{g mL}^{-1}$) and HL-60 ($\text{IC}_{50} = 1.2 \mu\text{g mL}^{-1}$) cells, respectively [101]. Eremophilane sesquiterpene compounds exhibit phytotoxic potential; antifungal, antibacterial, carcinostatic, and cytotoxic activities; and can act as a phytohormone [100,153].

Cytosporaphenone A (**50**), produced by the fungus *C. rhizophorae*, which is derived from *M. officinalis*, showed uncommon antiproliferative activity against MCF-7 and HepG-2 cell lines

at a concentration of 100 $\mu\text{g mL}^{-1}$, with inhibition rates of 91.0% and 80.5%, respectively [109]. The compounds **70** and **71** from the filamentous fungus *Alternaria* sp. reduced the viability of four human tumor cells lines: MCF-7, HepG-2, NCI-H460, and SF-268 with IC_{50} values ranging from 1.91 to 9.67 μM [110]. In addition, the multiforin I (**107**) produced by *N. discreta* showed moderate activity against lymphoma cells, reducing 70% cell growth [115].

Bioassay-guided fractionation of ethyl acetate extract from *D. pseudomangifera*, by cytotoxic effects against mammalian cancer cells allowed the isolation of the mycoepoxydien (**114**), which showed cytotoxic activity with IC_{50} values of 7.5, 17.7, and 15.8 μM against human uterine cervical carcinoma KB and MDA-MB-435 cells, respectively. The compound eremofortin F (**117**) was cytotoxic on KB ($\text{IC}_{50} = 13.9 \mu\text{M}$) and MRC5 ($\text{IC}_{50} = 12.2 \mu\text{M}$) cells [117]. The azaphilone mycoleptone B (**122**) isolated from *M. indicus* associated with *B. verticillata* presented cytotoxic activity against human prostate cancer (PC3) cells ($\text{IC}_{50} = 7.1 \pm 3.8 \mu\text{M}$). However, when compared with doxorubicin, the reference compound for cytotoxicity assays, its activity was lower [146]. Cercosporin (**177**), produced by *Mycosphaerella* sp. associated with *P. horizontalis*, showed lower cytotoxicity to mammalian Vero cells (1.54 μM) and high potency against MCF7 cancer cell lines ($\text{IC}_{50} = 4.68 \mu\text{M}$). The analog compound (**178**) was not active in these assays [136].

The compounds isolated from the endophytic fungus *T. koningiopsis* were evaluated for cytotoxic activity against HepG-2, MCF-7, SF-268 and A549 cells lines. The compounds koninginol B (**75**), 1R,3S,6S,7R,10S-7-isopropyl-4,10-dimethylbicyclo[4.4.0]dec-4-en-3,10-diol (**88**) and 1R,3R,6S,7R,10S-7-isopropyl-4,10-dimethylbicyclo[4.4.0]dec-4-en-3,10-diol (**89**) showed antiproliferative activities against A549 with IC_{50} values of 46.6, 31.3 and 22.2 μM , respectively [111]. However, none of the metabolites isolated from *T. spirale* (**91–96**) presented cytotoxicity activity against cancer cell lines [112].

The compounds from *D. lithocarpus*, another endophyte also isolated from *M. officinalis*, were tested for their cytotoxic activity by the sulforhodamine B method on four human tumor cell lines (SF-268, MCF-7, HepG-2 and A549). The compounds lithocarin B (**102**), lithocarin C (**103**), and tenellone H (**105**) presented IC_{50} values ranging from 30 to 100 μM in the four tumor cell lines selected [114].

Cancer human cell proliferation (SF-295 and HTC-116) was inhibited by 11-bromo-roquefortine D (**190**) with rates of 63% and 6.7%, at a concentration of 5.3 μM , respectively [141]. The cytotoxicity activity of 6-(heptacosyl-18'-Zeny)-2-(18''hydroxyl-1''enyl-19''oxy)-3-hydroxybenzoquinone (**202**) and (3 β -5 α -dihydroxy-6 β -phenylacetyloxy-ergosta-7, 22-diene) (**203**) was evaluated against a breast cancer cell line (MCF-7). They reduced the cell viability by 52% and 49%, respectively, at a concentration of 100 $\mu\text{g mL}^{-1}$ [145].

The PI3K α inhibitory activity of compounds isolated from *C. gloeosporioides*, an endophytic fungus from *U. rhynchophylla*, was evaluated. The phosphoinositide 3-kinases (PI3Ks), a family of lipid kinases, showed a crucial regulatory role in many cellular processes, including cell proliferation, especially PI3K α as one of the main targets for therapeutic intervention in cancer [154]. Hence, compounds from *C. gloeosporioides* were tested for their phosphoinositide 3-kinase (PI3K α) inhibitory activity. The compounds cyclo(L-leucyl-L-leucyl) (**149**) and brevianamide F (**150**) showed potent PI3K α inhibitory activity with IC_{50} values of 38.1 and 4.8 μM , respectively, while the other compounds showed weak activity at a concentration of 20 $\mu\text{g mL}^{-1}$ [127].

3.4. Anti-Inflammatory and Antioxidant Activity

Xylarenones C, D, F, and G (**14**, **15**, **17**, **18**) obtained from broth cultures by *Camarops* sp. showed meaningful inhibitory effect of reactive oxygen species (ROS) produced by stimulated neutrophils. The inhibitory concentrations of **14** ($\text{IC}_{50} = 6.13 \pm 0.41 \mu\text{M}$), **15** ($\text{IC}_{50} = 5.73 \pm 0.42 \mu\text{M}$), **17** ($\text{IC}_{50} = 5.90 \pm 0.70 \mu\text{M}$), and **18** ($\text{IC}_{50} = 4.17 \pm 0.81 \mu\text{M}$) were similar to those of quercetin and apocynin, an efficient inhibitor of the NADPH (nicotinamide adenine dinucleotide phosphate) oxidase complex. Furthermore, the compounds **14**, **15**, **17** and **18** were also evaluated for their radical scavenging properties in different analytical methods, such as scavengers of superoxide anions (the first ROS produced via the NADPH oxidase complex by stimulated neutrophils), HOCl (the main strong oxidant

produced by myeloperoxidase (MPO)), and MPO enzymatic activity, however, the compounds were inactive and had IC_{50} values of $>100 \mu\text{M}$ [100].

Colletopeptide A (**162**) isolated from *Colletotrichum* sp. showed significant anti-inflammatory activity; it inhibited the effects of lipopolysaccharide-induced nitric oxide production with an IC_{50} value of $8.3 \mu\text{M}$. The other colletopeptides, B (**163**), C (**164**) and D (**165**), also inhibited the lipopolysaccharide (LPS)-induced nitric oxide production, with IC_{50} values of 38.7, 13.5 and $22.2 \mu\text{M}$, respectively [130].

3.5. Anti-Protozoal Activity

Azaphilones mycoleptones A and B (**122–123**) and the polyketide austidiol (**125**) isolated from *M. indicus* presented in vitro leishmanicidal activity, being active against *Leishmania donovani*, with IC_{50} values of 28.5, 21.7 and $20.5 \mu\text{M}$, respectively [146].

The in vitro assay results suggest that cercosporin (**177**) is highly active against *Plasmodium falciparum* ($IC_{50} = 1.03 \mu\text{M}$), *L. donovani* ($IC_{50} = 0.46 \mu\text{M}$), and *Trypanosoma cruzi* ($IC_{50} = 1.08 \mu\text{M}$). Nevertheless, the bioactivity profile observed for cercosporin indicated that it was not specific for any the assayed parasites [127,128]. Compound **178**, identified as a seven-membered dioxepane ring-opened analogue of cercosporin, showed a significant reduction in activity in all these biological assays ($IC_{50} >10 \mu\text{g mL}^{-1}$), indicating the importance of the methylenedioxy functionality to the biological properties of compound **177** [136]. On the other hand, the alkaloid quinine (**118**) produced by *Diaporthe* sp. is a well-known antimalarial drug that is effective against the erythrocyte stage of the parasite *P. falciparum* [120,121,146].

3.6. Hyperglycemic Control

The best treatment for type 2 diabetes mellitus (TII-DM) involves hyperglycemic control using appropriate therapies. In recent years, substantial efforts to discover effective inhibitors of α -glucosidases from natural sources have been made [103,104]. The polyketide mimimoidione A (**34**) isolated from *S. minimoides* showed an excellent activity against *Saccharomyces cerevisiae* α -glucosidase (α -GHY), with an IC_{50} of $2.9 \mu\text{M}$ [104]. On the other hand, the tridepsides thielavins A (**42**), J (**43**) and K (**44**), isolated from *Chaetomium* sp. from *H. latiflora*, inhibited the α -GHY with IC_{50} values of 23.8, 15.8, and $22.1 \mu\text{M}$, respectively. Their inhibitory action was better than the acarbose standard ($IC_{50} = 545 \mu\text{M}$). Thielavin J (**43**) inhibited the activity of α -glucosidase from *B. stearothersophilus* (α GHBs) with an $IC_{50} = 30.5 \mu\text{M}$, being less active than acarbose ($IC_{50} = 0.015 \mu\text{M}$) [107]. The thielavin K (**44**) reduced fasting and postprandial glucose levels in a TII-DM animal model. Therefore, thielavin-type tridepsides represent a new class of α -glucosidase inhibitors and can become hypoglycemic agents for the treatment of TII-DM [107].

The compounds 3S,4R-(+)-4-hydroxymellein (**46**) and 3S,4S-(+)-4-hydroxymellein (**9**) inhibited the activity of enzyme *S. cerevisiae* α -glucosidase, with IC_{50} values of 441 ± 23 and $549 \pm 2.5 \mu\text{M}$, respectively [108]. Six compounds from *Alternaria* sp., namely, 2,4,8-trihydroxy-1-tetralone (**64**), 3,4-dihydro-3,4,8-trihydroxy-1[2H]-naphthalenone (**65**), 6-epi-stemphytriol (**69**), dihydroalterperyleneol (**70**), altertoxin II (**72**) and stemphyperyleneol (**73**), demonstrated prominent inhibitory activities against α -glucosidase (α GHY). The IC_{50} values in the range of 12.05 to $166.13 \mu\text{M}$, observed for these compounds, were clearly better and more significant when compared to the positive control of acarbose ($IC_{50} = 427.34 \mu\text{M}$) [110].

3.7. Other Activities

Proteases are relevant enzymatic targets because these proteins control the formation of functional peptides that participate in physiological processes [155]. The protease inhibitory activity of compounds xylarenones C–E (**14–16**) was evaluated in vitro using the enzymes subtilisin and pepsin. A potent inhibitory activity for the pepsin and subtilisin in protease assays was observed for compound **14** with an IC_{50} of 0.288 and $0.462 \mu\text{M}$, respectively. However, compounds **15** and **16** displayed no inhibitory activity on subtilisin ($<10\%$) at any of the four concentrations tested (1.00, 0.1, 0.01, and $0.001 \mu\text{M}$) [153].

Metabolites produced by *S. minimoides* were evaluated as potential human calmodulin (hCaM) inhibitors, and two compounds, 5-hydroxy-2,7-dimethoxy-8-methylnaphthoquinone (**33**) and vermelhotin (**41**), quenched the extrinsic fluorescence of this biosensor significantly, with dissociation constant (K_d) values of 1.55 μM and 0.25 μM, respectively. The docking displayed studies to predict the interaction of **33** with hCaM and many hydrophobic interactions with Phe19, Phe68, Met51, Met71, Met72 and Ile52. However, vermelhotin (**41**) showed hydrophobic interactions with Phe92, Met109, Met124, Glu127, Ala128, and Met144 [103,106].

4. Conclusions

As demonstrated in this paper, an increasing number of publications revealed a significant interest in endophytes from the Rubiaceae family in recent years due to pharmacological activities. This review presents the chemical diversity and pharmacological properties of secondary metabolites produced by endophyte fungi associated with various genera of Rubiaceae. Several classes of natural products are described for this endophyte, although this study highlights the importance of some metabolites which are involved in antifungal, antibacterial, and anti-protozoal activities; neurodegenerative diseases, cytotoxic activity, anti-inflammatory and antioxidant activity; and hyperglycemic control.

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References

1. Strobel, G.; Daisy, B. Bioprospecting for microbial endophytes and their natural products. *Microbiol. Mol. Biol. Rev.* **2003**, *67*, 491–502. [[CrossRef](#)] [[PubMed](#)]
2. Calixto, J.B. The role of natural products in modern drug discovery. *An. Acad. Bras. Cienc.* **2019**, *91* (Suppl. 3), e20190105. [[CrossRef](#)] [[PubMed](#)]
3. Singh, N.; Chandra, R. Endophytes: Unexplored reservoir of bioactive natural products. In *Handbook of Medicinal Plants and their Bioactive Compounds*; Gupta, N., Ed.; Research Signpost: Kerala, India, 2014; pp. 1–10.
4. Kaul, S.; Gupta, S.; Ahmed, M.; Dhar, M.K. Endophytic fungi from medicinal plants: A treasure hunt for bioactive metabolites. *Phytochem. Rev.* **2012**, *11*, 487–505. [[CrossRef](#)]
5. Newman, D.J.; Cragg, G.M. Natural products as sources of new drugs from 1981 to 2014. *J. Nat. Prod.* **2016**, *79*, 629–661. [[CrossRef](#)] [[PubMed](#)]
6. Newman, D.J.; Cragg, G.M. Natural products as sources of new drugs over the nearly four decades from 01/1981 to 09/2019. *J. Nat. Prod.* **2020**, *83*, 770–803. [[CrossRef](#)] [[PubMed](#)]
7. Gunatilaka, A.A.L. Natural products from plant-associated microorganisms: Distribution, structural diversity, bioactivity, and implications of their occurrence. *J. Nat. Prod.* **2006**, *69*, 509–526. [[CrossRef](#)]
8. Chandra, S. Endophytic fungi: Novel sources of anticancer lead molecules. *Appl. Microbiol. Biotechnol.* **2012**, *95*, 47–59. [[CrossRef](#)]
9. Martinez-Klimova, E.; Rodriguez-Pena, K.; Sanchez, S. Endophytes as sources of antibiotics. *Biochem. Pharmacol.* **2017**, *134*, 1–17. [[CrossRef](#)]
10. Barbero, M.; Artuso, E.; Prandi, C. Fungal anticancer metabolites: Synthesis towards drug discovery. *Curr. Med. Chem.* **2018**, *25*, 141–185. [[CrossRef](#)]
11. Lima, M.A.; de Oliveira, M.C.; Pimenta, A.; Uchoa, P. *Aspergillus niger*: A hundred years of contribution to the natural products chemistry. *J. Braz. Chem. Soc.* **2019**, *30*, 2029–2059. [[CrossRef](#)]
12. Torres-Mendoza, D.; Ortega, H.E.; Cubilla-Rios, L. Patents on endophytic fungi related to secondary metabolites and biotransformation applications. *J. Fungi* **2020**, *6*, 58. [[CrossRef](#)] [[PubMed](#)]
13. Azevedo, J.L. Microrganismos endofíticos. In *Ecologia Microbiana*; Melo, I.S., Azevedo, J.L., Eds.; Embrapa-CNPMA: Jaguariuna, Brazil, 1998; pp. 117–137.
14. Stone, J.; Bacon, C.W.; White, J.F. An overview of endophytic microbes: Endophytism defined. In *Microbial Endophytes*; Bacon, C.W., White, J.F., Eds.; Marcel Dekker Inc.: New York, NY, USA, 2000; pp. 3–29.

15. Kusari, S.; Hertweck, C.; Spiteller, M. Chemical ecology of endophytic fungi: Origins of secondary metabolites. *Chem. Biol.* **2012**, *19*, 792–798. [[CrossRef](#)] [[PubMed](#)]
16. Vasundhara, M.; Reddy, M.S.; Kumar, A. Secondary metabolites from endophytic fungi and their biological activities. In *New and Future Developments in Microbial Biotechnology and Bioengineering*; Elsevier: Amsterdam, The Netherlands, 2019; pp. 237–258. [[CrossRef](#)]
17. Guo, B.; Wang, Y.; Sun, X.; Tang, K. Bioactive natural products from endophytes: A review. *Appl. Biochem. Microbiol.* **2008**, *44*, 136–142. [[CrossRef](#)]
18. Dreyfuss, M.M.; Chapela, I.H. Fungi as producers of secondary metabolites. In *Discovery of Natural Products with Therapeutic Potential*; Gullo, V.P., Ed.; Butterworth-Heinemann: Boston, MA, USA, 1994; pp. 49–79.
19. Debbab, A.; Aly, A.H.; Proksch, P. Bioactive secondary metabolites from endophytes and associated marine derived fungi. *Fungal Divers.* **2011**, *49*, 1–12. [[CrossRef](#)]
20. Chapla, V.M.; Biasetto, C.R.; Araujo, A.R. Fungos endofíticos: Uma fonte inexplorada e sustentável de novos e bioativos produtos naturais. *Rev. Virtual Quim.* **2013**, *5*, 421–437. [[CrossRef](#)]
21. Schulz, B.; Boyle, C.; Draeger, S.; Römmert, A.K.; Krohn, K. Endophytic fungi: A source of novel biologically active secondary metabolites. *Mycol. Res.* **2002**, *106*, 996–1004. [[CrossRef](#)]
22. Zhang, H.W.; Song, Y.C.; Tan, R.X. Biology and chemistry of endophytes. *Nat. Prod. Rep.* **2006**, *23*, 753. [[CrossRef](#)]
23. Tan, R.X.; Zou, W.X. Endophytes: A rich source of functional metabolites (1987 to 2000). *Nat. Prod. Rep.* **2001**, *18*, 448–459. [[CrossRef](#)]
24. Gallo, M.B.C.; Guimarães, D.O.; Momesso, L.S.; Pupo, M.T. Natural products from endophytic fungi. In *Microbial Biotechnology*; Saikai, R., Bezbaruah, R.L., Bora, T.C., Eds.; New India Publishing Agency: New Delhi, India, 2007; pp. 139–168.
25. Martins, D.; Nunez, C. Secondary metabolites from Rubiaceae species. *Molecules* **2015**, *20*, 13422–13495. [[CrossRef](#)]
26. Pereira, Z.V.; Carvalho-Okano, R.M.; Garcia, F.C.P. Rubiaceae Juss. da Reserva Florestal Mata do Paraíso, Viçosa, MG, Brasil. *Acta Bot. Brasilica* **2006**, *20*, 207–224. [[CrossRef](#)]
27. Mongrand, S.; Badoc, A.; Patouille, B.; Lacomblez, C.; Chavent, M.; Bessoule, J.J. Chemotaxonomy of the Rubiaceae family based on leaf fatty acid composition. *Phytochemistry* **2005**, *66*, 549–559. [[CrossRef](#)] [[PubMed](#)]
28. Bolzani, V.D.S.; Young, M.C.M.; Furlan, M.; Cavalheiro, A.J.; Araújo, A.R.; Silva, D.H.S.; Lopes, M.N. Secondary metabolites from brazilian Rubiaceae plant species: Chemotaxonomical and biological significance. In *Recent Research Developments in Phytochemistry*; Pandalai, S.G., Ed.; Research Signpost: Kerala, India, 2001; Volume 5, pp. 19–31.
29. Cardoso, C.L.; Silva, D.H.S.; Young, M.C.M.; Castro-Gamboa, I.; Bolzani, V.D.S. Indole monoterpene alkaloids from *Chimarrhis turbinata* DC Prodr.: A contribution to the chemotaxonomic studies of the Rubiaceae family. *Rev. Bras. Farmacogn.* **2008**, *18*, 26–29. [[CrossRef](#)]
30. Rosa, E.A.; Silva, B.C.; Silva, F.M.; Tanaka, C.M.A.; Peralta, R.M.; Oliveira, C.M.A.; Kato, L.; Ferreira, H.D.; Silva, C.C. Flavonoides e atividade antioxidante em *Palicourea rigida* Kunth, Rubiaceae. *Rev. Bras. Farmacogn.* **2010**, *20*, 484–488. [[CrossRef](#)]
31. Rosales, P.F.; Bordin, G.S.; Gower, A.E.; Moura, S. Indole alkaloids: 2012 until now, highlighting the new chemical structures and biological activities. *Fitoterapia* **2020**, *143*, 104558. [[CrossRef](#)] [[PubMed](#)]
32. Soares, D.B.; Duarte, L.; Cavalcanti, A.; Silva, F.; Braga, A.; Lopes, M.T.; Takarashi, J.; Vieira-Filho, S. *Psychotria viridis*: Chemical constituents from leaves and biological properties. *An. Acad. Bras. Cienc.* **2017**, *89*, 927–938. [[CrossRef](#)] [[PubMed](#)]
33. Moreira, V.F.; Vieira, I.J.C.; Braz-Filho, R. Chemistry and biological activity of Condamineae tribe: A chemotaxonomic contribution of Rubiaceae family. *Am. J. Plant Sci.* **2015**, *6*, 2612–2631. [[CrossRef](#)]
34. Sweelam, H.M.; Abd-Alla, H.I.; Abdelwahab, A.B.; Gabr, M.M.; Kirsch, G. Secondary metabolites and biological activity of *Pentas* species: A minireview. *J. Adv. Res.* **2018**, *10*, 21–30. [[CrossRef](#)]
35. Dompeipen, E.J.; Srikandace, Y.; Suharso, W.P.; Cahyana, H.; Simanjunta, P. Potential endophytic microbes selection for antidiabetic bioactive compounds production. *Asian J. Biochem.* **2011**, *6*, 465–471. [[CrossRef](#)]
36. Handayani, D.; Sandrawati, N.; Ruslan, R.; Nestianda, O.; Fajrina, A.; Tallei, T.E. Cytotoxic and antimicrobial activities of ethyl acetate extract of mangrove plant *Scyphiphora hydrophyllacea* C. F. Gaertn—Associated fungi. *J. Appl. Pharm. Sci.* **2019**, *9*, 75–79. [[CrossRef](#)]

37. Qian, X.; Chen, L.; Guo, X.; He, D.; Shi, M.; Zhang, D. Shifts in community composition and co-occurrence patterns of phyllosphere fungi inhabiting *Mussaenda shikokiana* along an elevation gradient. *PeerJ* **2018**, *6*, e5767. [[CrossRef](#)]
38. Nasr, S.; Lutz, M.; Amoozegar, M.A.; Eparvier, V.; Stien, D.; Fazeli, S.A.S.; Yurkov, A. *Graphiola fimbriata*: The first species of Graphiolaceae (Exobasidiales, Basidiomycota) described only based on its yeast stage. *Mycol. Prog.* **2019**, *18*, 359–368. [[CrossRef](#)]
39. Oliveira, C.; Silva, G.; Bolzani, V.; Young, M.; Silva, D.; Lopes, M.; Araújo, A. Two new metabolites of an undescribed endophytic fungus belonging to the order Pleosporales isolated from *Alibertia macrophylla* (Rubiaceae). *Planta Med.* **2008**, *74*, 1057. [[CrossRef](#)]
40. Abdalla, M.A.; Aro, A.O.; Gado, D.; Passari, A.K.; Mishra, V.K.; Singh, B.P.; McGaw, L.J. Isolation of endophytic fungi from South African plants, and screening for their antimicrobial and extracellular enzymatic activities and presence of type I polyketide synthases. *South African J. Bot.* **2020**, 1–7. [[CrossRef](#)]
41. Ferreira, M.C.; de Assis, J.C.S.; Rosa, L.H. Diversity of endophytic fungi associated with *Carapichea ipecacuanha* from a native fragment of the Atlantic Rain Forest. *South African J. Bot.* **2020**. [[CrossRef](#)]
42. Lemaire, B.; Lachenaud, O.; Persson, C.; Smets, E.; Dessein, S. Screening for leaf-associated endophytes in the genus *Psychotria* (Rubiaceae). *FEMS Microbiol. Ecol.* **2012**, *81*, 364–372. [[CrossRef](#)]
43. Conti, R. Endophytic microorganisms from leaves of *Spermacoce verticillata* (L.): Diversity and antimicrobial activity. *J. Appl. Pharm. Sci.* **2012**, *2*, 17–22. [[CrossRef](#)]
44. de Lima, T.E.F.; Oliveira, R.J.V.; Neves, R.P.; Bezerra, J.L.; de Cavalcanti, M.A.Q. Endophytic yeasts of *Coffea arabica* and *Vitis labrusca* cv. Isabel from Pernambuco, Brazil. *Nov. Hedwigia* **2013**, *96*, 463–469. [[CrossRef](#)]
45. Wu, Y.; Girmay, S.; da Silva, V.M.; Perry, B.; Hu, X.; Tan, G.T. The role of endophytic fungi in the anticancer activity of *Morinda citrifolia* Linn. (Noni). *Evidence-Based Complement. Altern. Med.* **2015**, *2015*, 1–8. [[CrossRef](#)]
46. Sheik, S.; Chandrashekar, K.R.; Shirlal, S. Endophytic fungi associated with *Psychotria flavida* Talbot., an endemic plant of Western Ghats (India) and their bioactive potential. *Orient. Pharm. Exp. Med.* **2018**, *18*, 149–158. [[CrossRef](#)]
47. Liu, Y.; Bai, F.; Li, T.; Yan, H. An endophytic strain of genus *Paenibacillus* isolated from the fruits of Noni (*Morinda citrifolia* L.) has antagonistic activity against a Noni's pathogenic strain of genus *Aspergillus*. *Microb. Pathog.* **2018**, *125*, 158–163. [[CrossRef](#)]
48. Freire, E.S.; Campos, V.P.; Pinho, R.S.C.; Oliveira, D.F.; Faria, M.R.; Pohlit, A.M.; Noberto, N.P.; Rezende, E.L.; Pfenning, L.H.; Silva, J.R.C. Volatile substances produced by *Fusarium oxysporum* from coffee rhizosphere and other microbes affect *Meloidogyne incognita* and *Arthrobotrys conoides*. *J. Nematol.* **2012**, *44*, 321–328. [[PubMed](#)]
49. Chaves, F.C.; Gianfagna, T.J.; Aneja, M.; Posada, F.; Peterson, S.W.; Vega, F.E. *Aspergillus oryzae* NRRL 35191 from coffee, a non-toxic endophyte with the ability to synthesize kojic acid. *Mycol. Prog.* **2012**, *11*, 263–267. [[CrossRef](#)]
50. Casella, T.M.; Eparvier, V.; Mandavid, H.; Bendelac, A.; Odonne, G.; Dayan, L.; Duplais, C.; Espindola, L.S.; Stien, D. Antimicrobial and cytotoxic secondary metabolites from tropical leaf endophytes: Isolation of antibacterial agent pyrrocidine C from *Lewia infectoria* SNB-GTC2402. *Phytochemistry* **2013**, *96*, 370–377. [[CrossRef](#)] [[PubMed](#)]
51. Araujo, A.; Habeck, T.; Gubiani, J.; Silva, D.; Cavalheiro, A.; Bolzani, V. Phenolics compounds produced by *Camarops* sp. an endophytic fungus from *Alibertia macrophylla* (Rubiaceae). *Planta Med.* **2013**, *79*, 1182. [[CrossRef](#)]
52. Araujo, A.; Gubiani, J.; Cavalheiro, A.; Bolzani, V.D.S.; Nogueira, C. A new compound from *Camarops* sp. an endophytic fungus in *Alibertia macrophylla* (Rubiaceae). *Planta Med.* **2014**, *80*, 775. [[CrossRef](#)]
53. Chow, Y.; Ting, A.S.Y. Endophytic l-asparaginase-producing fungi from plants associated with anticancer properties. *J. Adv. Res.* **2015**, *6*, 869–876. [[CrossRef](#)]
54. Monteiro, M.C.P.; Alves, N.M.; Queiroz, M.V.; Pinho, D.B.; Pereira, O.L.; Souza, S.M.C.; Cardoso, P.G. Antimicrobial activity of endophytic fungi from coffee plants. *Biosci. J.* **2017**, 381–389. [[CrossRef](#)]
55. Mata, R.; Figueroa, M.; Rivero-Cruz, I.; Macias-Rubalcava, M.L. Insights in fungal bioprospecting in Mexico. *Planta Med.* **2018**, *84*, 594–605. [[CrossRef](#)]
56. Helfrich, E.J.N.; Piel, J. Biosynthesis of polyketides by trans-AT polyketide synthases. *Nat. Prod. Rep.* **2016**, *33*, 231–316. [[CrossRef](#)]

57. Fisch, K.M. Biosynthesis of natural products by microbial iterative hybrid PKS–NRPS. *RSC Adv.* **2013**, *3*, 18228. [[CrossRef](#)]
58. Crawford, J.M.; Townsend, C.A. New insights into the formation of fungal aromatic polyketides. *Nat. Rev. Microbiol.* **2010**, *8*, 879–889. [[CrossRef](#)] [[PubMed](#)]
59. Horsman, M.E.; Hari, T.P.A.; Boddy, C. Polyketide synthase and non-ribosomal peptide synthetase thioesterase selectivity: Logic gate or a victim of fate? *Nat. Prod. Rep.* **2016**, *33*, 183–202. [[CrossRef](#)] [[PubMed](#)]
60. Hur, G.H.; Vickery, C.R.; Burkart, M. Explorations of catalytic domains in non-ribosomal peptide synthetase enzymology. *Nat. Prod. Rep.* **2012**, *29*, 1074. [[CrossRef](#)] [[PubMed](#)]
61. Singh, M.; Chaudhary, S.; Sareen, D. Non-ribosomal peptide synthetases: Identifying the cryptic gene clusters and decoding the natural product. *J. Biosci.* **2017**, *42*, 175–187. [[CrossRef](#)]
62. Zhao, P.; Xue, Y.; Li, J.; Li, X.; Zu, X.; Zhao, Z.; Quan, C.; Gao, W.; Feng, S. Non-lipopeptide fungi-derived peptide antibiotics developed since 2000. *Biotechnol. Lett.* **2019**, *41*, 651–673. [[CrossRef](#)]
63. Mishra, A.; Choi, J.; Choi, S.J.; Baek, K.H. Cyclodipeptides: An overview of their biosynthesis and biological activity. *Molecules* **2017**, *22*, 1796. [[CrossRef](#)]
64. Nagano, N.; Umemura, M.; Izumikawa, M.; Kawano, J.; Ishii, T.; Kikuchi, M.; Tomii, K.; Kumagai, T.; Yoshimi, A.; Machida, M. Class of cyclic ribosomal peptide synthetic genes in filamentous fungi. *Fungal Genet. Biol.* **2016**, *86*, 58–70. [[CrossRef](#)]
65. Zhang, C.; Chen, X.; Orban, A.; Shukal, S.; Birk, F.; Too, H.P.; Rühl, M. Agroclybe aegerita serves as a gateway for identifying sesquiterpene biosynthetic enzymes in higher fungi. *ACS Chem. Biol.* **2020**, *15*, 1268–1277. [[CrossRef](#)]
66. Chen, Y.; Naresh, A.; Liang, S.; Lin, C.; Chein, R.; Lin, H. Discovery of a dual function cytochrome P450 that catalyzes enyne formation in cyclohexanoid terpenoid biosynthesis. *Angew. Chemie* **2020**, ange.202004435. [[CrossRef](#)]
67. Yamaguchi, S. Gibberellin metabolism and its regulation. *Annu. Rev. Plant Biol.* **2008**, *59*, 225–251. [[CrossRef](#)]
68. Fraley, A.E.; Sherman, D.H. Enzyme evolution in fungal indole alkaloid biosynthesis. *FEBS J.* **2020**, *287*, 1381–1402. [[CrossRef](#)]
69. Kishimoto, S.; Sato, M.; Tsunematsu, Y.; Watanabe, K. Evaluation of biosynthetic pathway and engineered biosynthesis of alkaloids. *Molecules* **2016**, *21*, 1078. [[CrossRef](#)]
70. Finefield, J.M.; Frisvad, J.C.; Sherman, D.H.; Williams, R.M. Fungal origins of the bicyclo[2.2.2]diazaoctane ring system of prenylated indole alkaloids. *J. Nat. Prod.* **2012**, *75*, 812–833. [[CrossRef](#)] [[PubMed](#)]
71. Li, S.M. Prenylated indole derivatives from fungi: Structure diversity, biological activities, biosynthesis and chemoenzymatic synthesis. *Nat. Prod. Rep.* **2010**, *27*, 57–78. [[CrossRef](#)] [[PubMed](#)]
72. Steffan, N.; Grundmann, A.; Yin, W.B.; Kremer, A.; Li, S.M. Indole prenyltransferases from fungi: A new enzyme group with high potential for the production of prenylated indole derivatives. *Curr. Med. Chem.* **2009**, *16*, 218–231. [[CrossRef](#)] [[PubMed](#)]
73. Xu, W.; Gavia, D.J.; Tang, Y. Biosynthesis of fungal indole alkaloids. *Nat. Prod. Rep.* **2014**, *31*, 1474–1487. [[CrossRef](#)]
74. Matsuda, Y.; Abe, I. Biosynthesis of fungal meroterpenoids. *Nat. Prod. Rep.* **2016**, *33*, 26–53. [[CrossRef](#)]
75. Mosunova, O.; Navarro-Muñoz, J.C.; Collemare, J. The biosynthesis of fungal secondary metabolites: From fundamentals to biotechnological applications. In *Encyclopedia of Mycology*; Elsevier: Amsterdam, The Netherlands, 2020; pp. 1–19. [[CrossRef](#)]
76. Keller, N.P. Fungal secondary metabolism: Regulation, function and drug discovery. *Nat. Rev. Microbiol.* **2019**, *17*, 167–180. [[CrossRef](#)]
77. Skellam, E. Strategies for Engineering Natural Product Biosynthesis in Fungi. *Trends Biotechnol.* **2019**, *37*, 416–427. [[CrossRef](#)]
78. Nielsen, J.C.; Nielsen, J. Development of fungal cell factories for the production of secondary metabolites: Linking genomics and metabolism. *Synth. Syst. Biotechnol.* **2017**, *2*, 5–12. [[CrossRef](#)]
79. Wisecaver, J.H.; Slot, J.C.; Rokas, A. The evolution of fungal metabolic pathways. *PLoS Genet.* **2014**, *10*, e1004816. [[CrossRef](#)] [[PubMed](#)]
80. Lim, F.Y.; Keller, N.P. Spatial and temporal control of fungal natural product synthesis. *Nat. Prod. Rep.* **2014**, *31*, 1277–1286. [[CrossRef](#)]
81. Wiemann, P.; Keller, N.P. Strategies for mining fungal natural products. *J. Ind. Microbiol. Biotechnol.* **2014**, *41*, 301–313. [[CrossRef](#)]

82. Craney, A.; Ahmed, S.; Nodwell, J. Towards a new science of secondary metabolism. *J. Antibiot. (Tokyo)* **2013**, *66*, 387–400. [[CrossRef](#)] [[PubMed](#)]
83. Brakhage, A.A.; Schroeckh, V. Fungal secondary metabolites—Strategies to activate silent gene clusters. *Fungal Genet. Biol.* **2011**, *48*, 15–22. [[CrossRef](#)] [[PubMed](#)]
84. Hoffmeister, D.; Keller, N.P. Natural products of filamentous fungi: Enzymes, genes, and their regulation. *Nat. Prod. Rep.* **2007**, *24*, 393–416. [[CrossRef](#)] [[PubMed](#)]
85. Lingappa, B.T. *Synchytrium borrieriae*, an endophytic alga. *Mycologia* **1956**, *48*, 427. [[CrossRef](#)]
86. Shibuya, H.; Kitamura, C.; Maehara, S.; Nagahata, M.; Winarno, H.; Simanjuntak, P.; Kim, H.-S.; Wataya, Y.; Ohashi, K. Transformation of Cinchona alkaloids into 1-N-oxide derivatives by endophytic *Xylaria* sp. isolated from *Cinchona pubescens*. *Chem. Pharm. Bull. (Tokyo)* **2003**, *51*, 71–74. [[CrossRef](#)]
87. Souza, A.Q.L.; Souza, A.D.L.; Astolfi Filho, S.; Pinheiro, M.L.B.; Sarquis, M.I.M.; Pereira, J.O. Atividade antimicrobiana de fungos endofíticos isolados de plantas tóxicas da amazônia: *Palicourea longiflora* (aubl.) rich e *Strychnos cogens* bentham. *Acta Amaz.* **2004**, *34*, 185–195. [[CrossRef](#)]
88. Jimenez-Salgado, T.; Fuentes-Ramirez, L.E.; Tapia-Hernandez, A.; Mascarua-Esparza, M.A.; Martinez-Romero, E.; Caballero-Mellado, J. *Coffea arabica* L., a new host plant for *Acetobacter diazotrophicus*, and isolation of other nitrogen-fixing acetobacteria. *Appl. Environ. Microbiol.* **1997**, *63*, 3676–3683. [[CrossRef](#)]
89. Ferreira, J.B.; de Abreu, M.S.; Pereira, I.S. Incidência de *Colletotrichum* spp. em frutos de *Coffea arabica* L. em diferentes estádios fisiológicos e tecidos do fruto maduro. *Ciência e Agrotecnologia* **2005**, *29*, 880–885. [[CrossRef](#)]
90. Peterson, S.W.; Vega, F.E.; Posada, F.; Nagai, C. *Penicillium coffeae*, a new endophytic species isolated from a coffee plant and its phylogenetic relationship to *P. fellutanum*, *P. thiersii* and *P. brocae* based on parsimony analysis of multilocus DNA sequences. *Mycologia* **2005**, *97*, 659–666. [[CrossRef](#)] [[PubMed](#)]
91. Santamaria, J.; Bayman, P. Fungal epiphytes and endophytes of Coffee leaves (*Coffea arabica*). *Microb. Ecol.* **2005**, *50*, 1–8. [[CrossRef](#)] [[PubMed](#)]
92. Vega, F.E.; Pava-Ripoll, M.; Posada, F.; Buyer, J.S. Endophytic bacteria in *Coffea arabica* L. *J. Basic Microbiol.* **2005**, *45*, 371–380. [[CrossRef](#)] [[PubMed](#)]
93. Strobel, G.A.; Ford, E.; Li, J.Y.; Sears, J.; Sidhu, R.S.; Hess, W.M. *Seimatoantlerium tepuiense* gen. nov., a unique epiphytic fungus producing taxol from the Venezuelan Guyana. *Syst. Appl. Microbiol.* **1999**, *22*, 426–433. [[CrossRef](#)]
94. Pandi, M.; Manikandan, R.; Muthumary, J. Anticancer activity of fungal taxol derived from *Botryodiplodia theobromae* Pat., an endophytic fungus, against 7, 12 dimethyl benz(a)anthracene (DMBA)-induced mammary gland carcinogenesis in Sprague dawley rats. *Biomed. Pharmacother.* **2010**, *64*, 48–53. [[CrossRef](#)]
95. Pandi, M.; Kumaran, R.S.; Choi, Y.K.; Kim, H.J.; Muthumary, J. Isolation and detection of taxol, an anticancer drug produced from *Lasiodiplodia theobromae*, an endophytic fungus of the medicinal plant *Morinda citrifolia*. *African J. Biotechnol.* **2011**, *10*, 1428–1435. [[CrossRef](#)]
96. Suresh, G.; Kokila, D.; Suresh, T.C.; Kumaran, S.; Velmurugan, P.; Vedhanayakisri, K.A.; Sivakumar, S.; Ravi, A.V. Mycosynthesis of anticancer drug taxol by *Aspergillus oryzae*, an endophyte of *Tarenna asiatica*, characterization, and its activity against a human lung cancer cell line. *Biocatal. Agric. Biotechnol.* **2020**, *24*, 101525. [[CrossRef](#)]
97. Cafeu, M.C.; Silva, G.H.; Teles, H.L.; Bolzani, V.D.S.; Araújo, A.R.; Young, M.C.M.; Pfenning, L.H. Substâncias antifúngicas de *Xylaria* sp., um fungo endofítico isolado de *Palicourea marcgravii* (Rubiaceae). *Quim. Nova* **2005**, *28*, 991–995. [[CrossRef](#)]
98. Oliveira, C.M.; Silva, G.H.; Regasini, L.O.; Zanardi, L.M.; Evangelista, A.H.; Young, M.C.M.; Bolzani, V.D.S.; Araújo, A.R. Bioactive metabolites produced by *Penicillium* sp.1 and sp.2, two endophytes associated with *Alibertia macrophylla* (Rubiaceae). *Zeitschrift für Naturforsch. C* **2009**, *64*, 824–830. [[CrossRef](#)]
99. Oliveira, C.M.; Regasini, L.O.; Silva, G.H.; Pfenning, L.H.; Young, M.C.M.; Berlinck, R.G.S.; Bolzani, V.D.S.; Araújo, A.R. Dihydroisocoumarins produced by *Xylaria* sp. and *Penicillium* sp., endophytic fungi associated with *Piper aduncum* and *Alibertia macrophylla*. *Phytochem. Lett.* **2011**, *4*, 93–96. [[CrossRef](#)]
100. Gubiani, J.R.; Zeraik, M.L.; Oliveira, C.M.; Ximenes, V.F.; Nogueira, C.R.; Fonseca, L.M.; Silva, D.H.S.; Bolzani, V.S.; Araújo, A.R. Biologically active eremophilane-type sesquiterpenes from *Camarops* sp., an endophytic fungus isolated from *Alibertia macrophylla*. *J. Nat. Prod.* **2014**, *77*, 668–672. [[CrossRef](#)] [[PubMed](#)]
101. Gubiani, J.R.; Nogueira, C.R.; Pereira, M.D.P.; Young, M.C.M.; Ferreira, P.M.P.; de Moraes, M.O.; Pessoa, C.; Bolzani, V.S.; Araújo, A.R. Rearranged sesquiterpenes and branched polyketides produced by the endophyte *Camarops* sp. *Phytochem. Lett.* **2016**, *17*, 251–257. [[CrossRef](#)]

102. Gubiani, J.R.; Habeck, T.R.; Chapla, V.M.; Silva, G.; Bolzani, V. da S.; Araújo, A.R. One stain-many compounds (OSMAC) method for production of phenolic compounds using *Camarops* sp., an endophytic fungus from *Alibertia macrophylla* (Rubiaceae). *Quim. Nova* **2016**, *39*, 1221–1224. [[CrossRef](#)]
103. Leyte-Lugo, M.; Figueroa, M.; Gonzalez, M.C.; Glenn, A.E.; González-Andrade, M.; Mata, R. Metabolites from the endophytic fungus *Sporormiella minimoides* isolated from *Hintonia latiflora*. *Phytochemistry* **2013**, *96*, 273–278. [[CrossRef](#)]
104. Rangel-Grimaldo, M.; Rivero-Cruz, I.; Madariaga-Mazon, A.; Figueroa, M.; Mata, R. α -Glucosidase inhibitors from *Preussia minimoides*. *J. Nat. Prod.* **2017**, *80*, 582–587. [[CrossRef](#)]
105. Leyte-Lugo, M.; Cerda-Garcia-Rojas, C.; Gonzalez, M.C.; Glenn, A.; Mata, R. 9S,11R-(+)-Ascosalitoxin from an endophytic fungus isolated from *Hintonia latiflora*. *Planta Med.* **2012**, *78*, 1157. [[CrossRef](#)]
106. Leyte-Lugo, M.; Gonzalez-Andrade, M.; Gonzalez, M.C.; Glenn, A.E.; Cerda-Garcia-Rojas, C.M.; Mata, R. (+)-Ascosalitoxin and vermelhotin, a calmodulin inhibitor, from an endophytic fungus isolated from *Hintonia latiflora*. *J. Nat. Prod.* **2012**, *75*, 1571–1577. [[CrossRef](#)]
107. Rivera-Chavez, J.; Gonzalez-Andrade, M.; Gonzalez, M.C.; Glenn, A.E.; Mata, R. Thielavins A, J and K: α -Glucosidase inhibitors from MEXU 27095, an endophytic fungus from *Hintonia latiflora*. *Phytochemistry* **2013**, *94*, 198–205. [[CrossRef](#)]
108. Rivera-Chavez, J.; Figueroa, M.; Gonzalez, M.C.; Glenn, A.E.; Mata, R. α -Glucosidase inhibitors from a *Xylaria feejeensis* associated with *Hintonia latiflora*. *J. Nat. Prod.* **2015**, *78*, 730–735. [[CrossRef](#)]
109. Liu, H.X.; Tan, H.B.; Liu, Y.; Chen, Y.C.; Li, S.N.; Sun, Z.H.; Li, H.H.; Qiu, S.X.; Zhang, W.M. Three new highly-oxygenated metabolites from the endophytic fungus *Cytospora rhizophorae* A761. *Fitoterapia* **2017**, *117*, 1–5. [[CrossRef](#)] [[PubMed](#)]
110. Wang, Y.; Liu, H.X.; Chen, Y.C.; Sun, Z.H.; Li, H.H.; Li, S.N.; Yan, M.L.; Zhang, W.M. Two new metabolites from the endophytic fungus *Alternaria* sp. A744 derived from *Morinda officinalis*. *Molecules* **2017**, *22*, 765. [[CrossRef](#)] [[PubMed](#)]
111. Chen, S.; Li, H.; Chen, Y.; Li, S.; Xu, J.; Guo, H.; Liu, Z.; Zhu, S.; Liu, H.; Zhang, W. Three new diterpenes and two new sesquiterpenoids from the endophytic fungus *Trichoderma koningiopsis* A729. *Bioorg. Chem.* **2019**, *86*, 368–374. [[CrossRef](#)] [[PubMed](#)]
112. Chen, S.; Liu, H.; Liu, Z.; Li, S.; Chen, Y.; Li, H.; Li, D.; Zhang, W. Two new polyketide compounds from the endophytic fungus *Trichoderma spirale* A725 of *Morinda officinalis*. *Chin. J. Org. Chem.* **2020**. [[CrossRef](#)]
113. Liu, H.X.; Tan, H.B.; Chen, K.; Zhao, L.Y.; Chen, Y.C.; Li, S.N.; Li, H.H.; Zhang, W. Cytosporins A–D, novel benzophenone derivatives from the endophytic fungus *Cytospora rhizophorae* A761. *Org. Biomol. Chem.* **2019**, *17*, 2346–2350. [[CrossRef](#)]
114. Liu, H.; Chen, Y.; Li, H.; Li, S.; Tan, H.; Liu, Z.; Li, D.; Liu, H.; Zhang, W. Four new metabolites from the endophytic fungus *Diaporthe lithocarpus* A740. *Fitoterapia* **2019**, *137*, 104260. [[CrossRef](#)]
115. Sowemimo, A.A.; Edrada-Ebel, R.; Ebel, R.; Proksch, P.; Omobuwajo, O.R.; Adesanya, S.A. Major constituents of the predominant endophytic fungi from the Nigerian plants *Bryophyllum Pinnatum*, *Morinda Lucida* and *Jathropa Gossypifolia*. *Nat. Prod. Commun.* **2008**, *3*, 1934578X0800300. [[CrossRef](#)]
116. Chomcheon, P.; Wiyakrutta, S.; Aree, T.; Sriubolmas, N.; Ngamrojanavanich, N.; Mahidol, C.; Ruchirawat, S.; Kittakoop, P. Curvularides A–E: Antifungal hybrid peptide-polyketides from the endophytic fungus *Curvularia geniculata*. *Chem. A Eur. J.* **2010**, *16*, 11178–11185. [[CrossRef](#)]
117. Mandavid, H.; Rodrigues, A.M.S.; Espindola, L.S.; Eparvier, V.; Stien, D. Secondary metabolites isolated from the Amazonian endophytic fungus *Diaporthe* sp. SNB-GSS10. *J. Nat. Prod.* **2015**, *78*, 1735–1739. [[CrossRef](#)]
118. Maehara, S.; Simanjuntak, P.; Ohashi, K.; Shibuya, H. Composition of endophytic fungi living in *Cinchona ledgeriana* (Rubiaceae). *J. Nat. Med.* **2010**, *64*, 227–230. [[CrossRef](#)]
119. Maehara, S.; Simanjuntak, P.; Kitamura, C.; Ohashi, K.; Shibuya, H. *Cinchona* alkaloids are also produced by an endophytic filamentous fungus living in *Cinchona* plant. *Chem. Pharm. Bull. (Tokyo)* **2011**, *59*, 1073–1074. [[CrossRef](#)] [[PubMed](#)]
120. Maehara, S.; Simanjuntak, P.; Kitamura, C.; Ohashi, K.; Shibuya, H. Bioproduction of *Cinchona* alkaloids by the endophytic fungus *Diaporthe* sp. associated with *Cinchona ledgeriana*. *Chem. Pharm. Bull.* **2012**, *60*, 1301–1304. [[CrossRef](#)] [[PubMed](#)]
121. Maehara, S.; Agusta, A.; Kitamura, C.; Ohashi, K.; Shibuya, H. Composition of the endophytic filamentous fungi associated with *Cinchona ledgeriana* seeds and production of *Cinchona* alkaloids. *J. Nat. Med.* **2016**, *70*, 271–275. [[CrossRef](#)]

122. Maehara, S.; Agusta, A.; Tokunaga, Y.; Shibuya, H.; Hata, T. Endophyte composition and Cinchona alkaloid production abilities of Cinchona ledgeriana cultivated in Japan. *J. Nat. Med.* **2019**, *73*, 431–438. [[CrossRef](#)]
123. Radiastuti, N.; Mutea, D.; Sumarlin, L.O. Endophytic Colletotrichum spp. from Cinchona calisaya wedd. and its potential quinine production as antibacterial and antimalaria. In *AIP Conference Proceedings 19–21 October 2016, East Kalimantan, Indonesia*; AIP Publishing: Melville, NY, USA, 2017; p. 020022. [[CrossRef](#)]
124. Wei, B.; Yang, Z.D.; Chen, X.W.; Zhou, S.Y.; Yu, H.T.; Sun, J.Y.; Yao, X.J.; Wang, Y.G.; Xue, H.Y. Colletotrilactam A–D, novel lactams from Colletotrichum gloeosporioides GT-7, a fungal endophyte of Uncaria rhynchophylla. *Fitoterapia* **2016**, *113*, 158–163. [[CrossRef](#)]
125. Chen, X.W.; Yang, Z.D.; Sun, J.H.; Song, T.T.; Zhu, B.Y.; Zhao, J.W. Colletotrichine A, a new sesquiterpenoid from Colletotrichum gloeosporioides GT-7, a fungal endophyte of Uncaria rhynchophylla. *Nat. Prod. Res.* **2018**, *32*, 880–884. [[CrossRef](#)] [[PubMed](#)]
126. Chen, X.W.; Yang, Z.D.; Li, X.F.; Sun, J.H.; Yang, L.J.; Zhang, X.G. Colletotrichine B, a new sesquiterpenoid from Colletotrichum gloeosporioides GT-7, a fungal endophyte of Uncaria rhynchophylla. *Nat. Prod. Res.* **2019**, *33*, 108–112. [[CrossRef](#)] [[PubMed](#)]
127. Yang, Z.D.; Li, Z.J.; Zhao, J.W.; Sun, J.H.; Yang, L.J.; Shu, Z.M. Secondary metabolites and PI3K inhibitory activity of Colletotrichum gloeosporioides, a fungal endophyte of Uncaria rhynchophylla. *Curr. Microbiol.* **2019**, *76*, 904–908. [[CrossRef](#)]
128. Andre, A.; Wojtowicz, N.; Toure, K.; Stien, D.; Eparvier, V. New acorane sesquiterpenes isolated from the endophytic fungus Colletotrichum gloeosporioides SNB-GSS07. *Tetrahedron Lett.* **2017**, *58*, 1269–1272. [[CrossRef](#)]
129. Numponsak, T.; Kumla, J.; Suwannarach, N.; Matsui, K.; Lumyong, S. Biosynthetic pathway and optimal conditions for the production of indole-3-acetic acid by an endophytic fungus, Colletotrichum fructicola. *PLoS ONE* **2018**, *13*, e0205070. [[CrossRef](#)]
130. Feng, L.; Wang, J.; Liu, S.; Zhang, X.J.; Bi, Q.R.; Hu, Y.Y.; Wang, Z.; Tan, N.H. Colletopeptides A–D, anti-inflammatory cyclic tridepsipeptides from the plant endophytic fungus Colletotrichum sp. S8. *J. Nat. Prod.* **2019**, *82*, 1434–1441. [[CrossRef](#)]
131. Zheng, B.; Zeng, Y.B.; Dai, H.F.; Zuo, W.J.; Guo, Z.K.; Yang, T.; Zhong, H.M.; Mei, W.L. Two new meroterpenes from endophytic fungus A1 of Scyphiphora hydrophyllacea. *J. Asian Nat. Prod. Res.* **2012**, *14*, 776–779. [[CrossRef](#)]
132. Mei, W.L.; Zheng, B.; Zhao, Y.X.; Zhong, H.M.; Chen, X.L.W.; Zeng, Y.B.; Dong, W.H.; Huang, J.L.; Proksch, P.; Dai, H.F. Meroterpenes from endophytic fungus A1 of Mangrove plant Scyphiphora hydrophyllacea. *Mar. Drugs* **2012**, *10*, 1993–2001. [[CrossRef](#)] [[PubMed](#)]
133. Zeng, Y.B.; Wang, H.; Zuo, W.J.; Zheng, B.; Yang, T.; Dai, H.; Mei, W.L. A fatty acid glycoside from a marine-derived fungus isolated from Mangrove plant Scyphiphora hydrophyllacea. *Mar. Drugs* **2012**, *10*, 598–603. [[CrossRef](#)] [[PubMed](#)]
134. Zeng, Y.B.; Dai, H.F.; Huang, J.L.; Mei, W.L. Separation, purification and structural elucidation of the bio-active components from fermentation broth of endophytic fungus C22 from Scyphiphora hydrophyllacea. *Chin. J. Antibiot.* **2011**, *36*, 276–279.
135. Martinez-Luis, S.; Cherigo, L.; Higginbotham, S.; Arnold, E.; Spadafora, C.; Ibañez, A.; Gerwick, W.H.; Cubilla-Rios, L. Screening and evaluation of antiparasitic and in vitro anticancer activities of Panamanian endophytic fungi. *Int. Microbiol.* **2011**, *14*, 95–102. [[CrossRef](#)]
136. Moreno, E.; Varughese, T.; Spadafora, C.; Arnold, E.; Coley, P.D.; Gerwick, W.H.; Cubilla-Rios, L. Chemical constituents of the new endophytic fungus Mycosphaerella sp. nov. and their anti-parasitic activity. *Nat. Prod. Commun.* **2011**, *6*, 835–840.
137. Da Silva, B.F.; Rodrigues-Filho, E. Production of a benzylated flavonoid from 5,7,3',4',5'-pentamethoxyflavanone by Penicillium griseooreum. *J. Mol. Catal. B Enzym.* **2010**, *67*, 184–188. [[CrossRef](#)]
138. da Silva, J.V.; Fill, T.P.; da Silva, B.F.; Rodrigues-Filho, E. Diclavatol and tetronic acids from Penicillium griseooreum. *Nat. Prod. Res.* **2013**, *27*, 9–16. [[CrossRef](#)]
139. Vega, F.E.; Posada, F.; Peterson, S.W.; Gianfagna, T.J.; Chaves, F. Penicillium species endophytic in coffee plants and ochratoxin A production. *Mycologia* **2006**, *98*, 31–42. [[CrossRef](#)]
140. Valente, A.M.M.P.; Ferreira, A.G.; Daolio, C.; Rodrigues Filho, E.; Boffo, E.F.; Souza, A.Q.L.; Sebastianes, F.L.S.; Melo, I.S. Production of 5-hydroxy-7-methoxy-4-methylphthalide in a culture of Penicillium crustosum. *An. Acad. Bras. Cienc.* **2013**, *85*, 487–496. [[CrossRef](#)] [[PubMed](#)]

141. da Silva, J.V.; Fill, T.P.; Lotufo, L.V.; Pessoa, C.O.; Rodrigues-Filho, E. Biosynthesis of bromoroquefortines in a high saline medium by *Penicillium chrysogenum*, a terrestrial endophyte collected from *Coffea arabica*. *Helv. Chim. Acta* **2014**, *97*, 1345–1353. [[CrossRef](#)]
142. Forcina, G.C.; Castro, A.; Bokesch, H.R.; Spakowicz, D.J.; Legaspi, M.E.; Kucera, K.; Villota, S.; Narváez-Trujillo, A.; McMahon, J.B.; Gustafson, K.R.; et al. Stelligosphaerols A and B, sesquiterpene-polyol conjugates from an Ecuadorian fungal endophyte. *J. Nat. Prod.* **2015**, *78*, 3005–3010. [[CrossRef](#)]
143. Abreu, L.M.; Costa, S.S.; Pfenning, L.H.; Takahashi, J.A.; Larsen, T.O.; Andersen, B. Chemical and molecular characterization of Phomopsis and Cytospora-like endophytes from different host plants in Brazil. *Fungal Biol.* **2012**, *116*, 249–260. [[CrossRef](#)] [[PubMed](#)]
144. Shylaja, G.; Sasikumar, K.; Sathivelu, A. Antimycobacterial potential of resorcinol type lipid isolated from *Chaetomium cupreum*, an endophytic fungus from *Mussaenda luteola*. *Bangladesh J. Pharmacol.* **2018**, *13*, 114–119. [[CrossRef](#)]
145. Shylaja, G.; Sathivelu, A. Evaluation of bioactive metabolites isolated from endophytic fungus *Chaetomium cupreum* of the plant *Mussaenda luteola*. *Indian J. Pharm. Educ. Res.* **2019**, *53*, s255–s263. [[CrossRef](#)]
146. Andrioli, W.J.; Conti, R.; Araujo, M.J.; Zanasi, R.; Cavalcanti, B.C.; Manfrim, V.; Toledo, J.S.; Tedesco, D.; De Moraes, M.O.; Pessoa, C. Mycoleptones A–C and polyketides from the endophyte *mycoleptodiscus indicus*. *J. Nat. Prod.* **2014**, *77*, 70–78. [[CrossRef](#)]
147. Teles, A.P.C.; Takahashi, J.A. Paecilomide, a new acetylcholinesterase inhibitor from *Paecilomyces lilacinus*. *Microbiol. Res.* **2013**, *168*, 204–210. [[CrossRef](#)]
148. Wang, Z.; Ma, Z.; Wang, L.; Tang, C.; Hu, Z.; Chou, G.X.; Li, W. Active anti-acetylcholinesterase component of secondary metabolites produced by the endophytic fungi of *Huperzia serrata*. *Electron. J. Biotechnol.* **2015**, *18*, 399–405. [[CrossRef](#)]
149. Li, Z.; Ma, N.; Zhao, P.J. Acetylcholinesterase inhibitory active metabolites from the endophytic fungus *Colletotrichum* sp. YMF432. *Nat. Prod. Res.* **2019**, *33*, 1794–1797. [[CrossRef](#)]
150. Lee, H.W.; Kim, Y.J.; Nam, S.J.; Kim, H. Potent selective inhibition of monoamine oxidase A by alternariol monomethyl ether isolated from *Alternaria brassicae*. *J. Microbiol. Biotechnol.* **2017**, *27*, 316–320. [[CrossRef](#)] [[PubMed](#)]
151. Youdim, M.B.H.; Edmondson, D.; Tipton, K.F. The therapeutic potential of monoamine oxidase inhibitors. *Nat. Rev. Neurosci.* **2006**, *7*, 295–309. [[CrossRef](#)] [[PubMed](#)]
152. Herraiz, T.; González, D.; Ancin-Azpilicueta, C.; Aran, V.J.; Guillen, H. β -Carboline alkaloids in *Peganum harmala* and inhibition of human monoamine oxidase (MAO). *Food Chem. Toxicol.* **2010**, *48*, 839–845. [[CrossRef](#)] [[PubMed](#)]
153. Oliveira, C.M.; Silva, G.H.; Regasini, L.O.; Flausino, O.; Lopez, S.N.; Abissi, B.M.; Berlinck, R.G.S.; Sette, L.D.; Bonugli-Santos, R.C.; Rodrigues, A. Xylarenones C–E from an endophytic fungus isolated from *Alibertia macrophylla*. *J. Nat. Prod.* **2011**, *74*, 1353–1357. [[CrossRef](#)]
154. Liu, P.; Cheng, H.; Roberts, T.M.; Zhao, J.J. Targeting the phosphoinositide 3-kinase pathway in cancer. *Nat. Rev. Drug Discov.* **2009**, *8*, 627–644. [[CrossRef](#)]
155. Tomasselli, A.G.; Heinrikson, R.L. Targeting the HIV-protease in AIDS therapy: A current clinical perspective. *Biochim. Biophys. Acta Protein Struct. Mol. Enzymol.* **2000**, *1477*, 189–214. [[CrossRef](#)]

