Review

Structural Diversity and Biological Activities of Novel Secondary Metabolites from Endophytes

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Abstract: Exploration of structurally novel natural products greatly facilitates the discovery of biologically active pharmacophores that are biologically validated starting points for the development of new drugs. Endophytes that colonize the internal tissues of plant species, have been proven to produce a large number of structurally diverse secondary metabolites. These molecules exhibit remarkable biological activities, including antimicrobial, anticancer, anti-inflammatory and antiviral properties, to name but a few. This review surveys the structurally diverse natural products with new carbon skeletons, unusual ring systems, or rare structural moieties that have been isolated from endophytes between 1996 and 2016. It covers their structures and bioactivities. Biosynthesis and/or total syntheses of some important compounds are also highlighted. Some novel secondary metabolites with marked biological activities might deserve more attention from chemists and biologists in further studies.

Keywords: endophytes; natural products; skeletons; biosynthesis; bioactivities

1. Introduction

The last 30 years have seen tremendous successes in natural product-based drug discovery [1,2]. Natural products, their semisynthetic derivatives, and synthetic products that mimic a natural product template, represent more than half of all approved small-molecule drugs [1,3]. Diverse and biologically active pharmacophores, especially in naturally occurring novel compounds, play a pivotal role in modern drug discovery [4,5]. They possess specific steric and electronic properties for molecular recognition by a biological target [6]. Alarmingly, only a few new natural product drug pharmacophores have been discovered in the last twenty years, which poses critical issues for natural product-driven lead discovery campaigns and new drug types [7].

Many strategies have been developed to discover structurally novel natural product leads through available biological approaches [8]. Mining the largely unexplored natural sources, such as endophytes, will pave the way for chemical and biological novelties [8]. Endophytes, mainly fungi and bacteria, colonize the living, internal plant tissues without causing visible symptoms of disease [9]. There are approximately 300,000 different plant species inhabiting our planet and it can be expected that each individual one has a complex community of one to many cultivable or uncultivable endophytic microorganisms [10,11]. Endophytes are recognized to have complex associations with host plants and other organisms, including endophytic microorganisms in their ecological niches and pathogens in external environments [12–14]. In order to adapt to their microenvironments, endophytes typically coevolve a plethora of traits that range from production of diverse chemical defense compounds to triggers for activating cryptic biosynthetic pathways,
production of precursors, quorum sensing molecules, epigenetic modulators, and even direct physical organismal interactions [15,16]. These functional biomolecules derived from endophytes are important from an ecological perspective [13]. For instance, the endophytic fungus *Neotyphodium coenophialum* inhabiting the tall fescue (*Festuca arundinacea*) was discovered to produce toxic alkaloids, defending host plants against herbivorous mammals and causing “fescue toxicosis” of livestock [17]. From the medicinal perspective, they may directly or indirectly be used as therapeutic agents against numerous diseases.

The enormous diversity of endophytes in combination with their potential biosynthetic capabilities has provided the impetus for a number of chemical investigations on endophytes. Endophytes are now well-known to biosynthesize diverse natural products with intriguing biological activities, and around ten reviews have reported on the new and known bioactive secondary metabolites of endophytes [18–27]. It should be noted that small molecules with new carbon skeletons, unusual ring systems, or rare structural moieties from endophytic fungi and bacteria have not been reviewed to the best of our knowledge. They might deserve attention from chemists and biologists and could be a potential resource of new biologically active pharmacophores for natural product-based drug development.

The target of this review is to summarize endophyte-derived secondary metabolites with new carbon skeletons, unique ring systems, or uncommon structural moieties isolated in a period between 1996 and 2016 that marks enormous progress in the chemical investigation of fungal and bacterial endophytes. Their structures and biological activities, together with the biosynthesis and total syntheses of some important molecules are described. In this review, the structures are mainly classified according to their proposed biosynthesis. They might be further arranged according to the structural features of secondary metabolites.

2. Polyketides

2.1. Macrolides

A mangrove-derived bacterial endophyte *Streptomyces* sp. was discovered by the Hertweck group to produce four unprecedented ansa macrolides, divergolides A–D (1–4, Figure 1) [28,29].

![Figure 1. Structures of divergolides A–D (1–4).](image-url)
They were biosynthesized from a common linear polyketide precursor that underwent various reactions including an optional acyl migration to form the diverse multicyclic structures (Scheme 1). An unusual isobutylmalonyl-CoA (ibMCoA) extender unit derived from isobutyrate and acetate rather than l-leucine was involved in the divergolide polyketide pathway (Scheme 1) [30]. The remarkable structural plasticity of this kind of macrolides led to different antibacterial and cytotoxic properties [31]. Compound 1 showed the strongest antibacterial activity against *Mycobacterium vaccae* with an inhibitory zone of 19 mm at 50 µg per paper disk in the disk diffusion assay, while compound 4 demonstrated marked cytotoxicity against several cancer cell lines, with IC_{50} values ranging from 1.0 to 2.0 µM [28]. Their intriguing structures and associated antibacterial or antitumor activities have stimulated various synthetic methods towards divergolides [32,33], and scientific interest in biosynthetic gene clusters [29].

**Scheme 1.** The proposed biosynthetic pathway for divergolides A–D (1–4), starting from the ansamycin starter unit AHBA. The polyketide backbone is proposed to be disrupted through a putative Baeyer-Villiger oxidation.

Iwatsuki and co-workers obtained a fungus *Actinoallomurus fulvus* harbored in the roots of *Capsicum frutescens* collected in Thailand [34]. Chemical investigation of this fungus led to the discovery of five unique 12-membered macrolides, actinoallolides A–E (5–9, Figure 2). Compound 5 exhibited significant anti-trypanosomal activity against *Trypanosoma cruzi* (IC_{50}: 0.226 µg/mL) similar to that of commonly used therapeutic drug, benznidazole (IC_{50}: 0.418 µg/mL), indicating a promising new class of lead compounds for treating Chagas disease [34]. Bioassay-guided isolation of the ethyl acetate extract of an unidentified endophytic fungus provided an unusual C_{16} nonenolide, microcarpalide (10) (Figure 2) with an alky side chain. Compound 10 disrupted microfilaments in approximately half of the cells at a concentration of 0.5–1.0 µg/mL and showed weak cytotoxicity against two mammalian cell lines (KB and LoVo) [35].
2.2. Benzopyran

The Krohn group discovered seven rare chromanones, blennolides A–G (11–17, Figure 3) from an endophytic fungus Blennoria sp. occurring in Carpobrotus edulis found in the Canary Islands [36]. They displayed moderate antialgal activity against Chlorella fusca and antifungal activity against Microbotryum violaceum with radii of the zones of inhibition ranging from 5 to 9 mm with 50 μg per paper disk in the agar diffusion assay. Compounds 14–16 are unique natural products with a highly substituted γ-lactone moiety, while compound 17 is a novel heterodimer incorporating two unusual chromanone subunits, the monomer 11 and the deoxy analogue of monomer 15 [36]. Another unusual heterodimeric chromanone, noduliprevenone (18) (Figure 3), was isolated from a Mediterranean alga-derived endophyte Nodulisporium sp., and was a potential competitive inhibitor of cytochrome P450 1A with an IC₅₀ value 6.5 ± 1.6 μM [37].
Figure 4) with a unique oxepino[2,3-b] chromen-6-one (ring-enlarged xanthone) skeleton from an endophyte Microsphaeropsis sp. isolated from the shoots of Lycium intricatum [38]. From an endophytic Chalara sp. isolated from the plant Artemisia vulgaris, isofusidienol A–D (22–25) (Figure 4) with an unprecedented chromone-3-oxepine moiety were found by the Zeeck group. Compounds 22 and 23 exhibited strong antibacterial activity against Bacillus subtilis with inhibition zones of 23 and 22 mm at 15 μg/disk, respectively [39]. Lycopodiellactone (26, Figure 4) with an uncommon δ-lactone and a rare 3-methylene isochromanone moiety, was obtained from a fungal endophyte Paraphaeosphaeria neglecta isolated from a Hawaiian indigenous plant, Lycopodiella cernua [40]. This metabolite might be biosynthesized by a polyketide pathway involving a key condensation of the δ-lactone and the 3-methylene isochromanone motif.

![Microsphaeropsone A (19) R = OH](image1)

![Microsphaeropsone B (20) R = H](image2)

![Isofusidienol A (22) R = H, Δ unsaturated](image3)

![Isofusidienol B (23) R = OH, Δ unsaturated](image4)

![Isofusidienol C (24) R = H](image5)

![Isofusidienol D (25) R = OH](image6)

![Lycopodiellactone (26)](image7)

**Figure 4.** Structures of microsphaeropsones A–C (19–21), isofusidienols A–D (22–25) and lycopodiellactone (26).

### 2.3. Spiro Compounds

Chemical investigation of the EtOAc extract of an endophytic fungus Pestalotiopsis virgatula led to the isolation of three cytotoxic metabolites named virgatolides A–C (27–29, Figure 5) [41]. They are new members of the rare benzannulated 6,6-spiroketal class of natural products and possess one or two γ-lactone units, representing the first occurrence of the γ-lactone units in the benzannulated 6,6-spiroketals. Jaroszewski and co-workers employed a hyphenated technique comprising HPLC-SPE-NMR to uncover some novel metabolites from Pestalotiopsis virgatula, an endophyte inhabiting the bark of Terminalia chebula [42,43]. Among them, pestalospiranes A and B (30 and 31, Figure 5) have an unprecedented 1,9,11,18-tetraoxadispiro[6.2.6.2]octadecane skeleton in addition to the characteristic benzocyclic oxepin motif [43,44]. A bioinspired tandem dimerization-spiroketalization strategy to forge the unique dispiro skeleton of 31 has recently been described (Scheme 2) [44].

The Munro group from New Zealand disclosed the structure of spiro-mamakone A (32, Figure 5) from a non-sporulating endophytic fungus derived from the New Zealand native tree Knightia excels [45]. This compound belongs to the family of the structurally diverse spirobisnaphthalenes and represents the first spirobisnaphthalene analogue containing a new spiro-nonadiene skeleton [45]. Using feeding experiments conducted with different labeled
acetates, the biosynthesis of compound 32 was investigated and found to involve the same two pentaketide-derived naphthalene units that underwent oxidative coupling and further extensive rearrangement [46]. Compound 32 exhibited significant cytotoxicity toward the P388 murine leukemia cell line (IC_{50} of 0.33 μM), and was also active against three selected bacteria [45]. A series of spiro-mamakone analogues have been synthesized for the investigation of structure-activity relationships, confirming the importance of the enedione moiety to bioactivities [47]. Penicillactones A–C (33–35, Figure 5) were biosynthesized by an endophytic fungus, _Penicillium dangeardii_ residing in the plant _Lysidice rhodostegia_, and are novel natural products possessing a spirocyclic anhydride moiety [48]. Compounds 34 and 35 were active in inhibiting the release of β-glucuronidase from polymorphonuclear leukocytes with ED_{50} values of 2.58 and 1.57 μM, respectively.

\[ \text{Scheme 2. Bioinspired tandem dimerization-spiroketalization for the total synthesis of pestalospirane B (31).} \]

2.4. Quinones

In 1995, Clardy and co-workers identified an endophytic fungus _Pestalotiopsis microspora_, which lived in the inner bark of the healthy host plant _Torreya taxifolia_ but could be switched to have the pathological activity by environmental triggers [49]. Bioassay-guided investigation of the fermentation culture of _P. microspora_ led to the isolation of an unusual dimeric quinone, (±)-torreyanic acid (36, Figure 6) [50]. Compound 36, as a cytotoxic agent, caused cell death by apoptosis with IC_{50}
values ranging from 5.1 to 65.0 μM for 25 different human cell lines [50]. Inspired by a proposed biosynthetic scheme of 36, the Porco, Jr. and Mehta groups successfully applied a biomimetic electrocyclization/Diels-Alder dimerization cascade to construct the structure of 36 [51,52]. Ding et al. isolated and identified a novel torreyanic acid analogue (37, Figure 6) from a fungus Pestalotiopsis sp. inhabiting the lichen Clavaroids sp. [53].

![Torreyanic acid (36) and Torreyanic acid analogue (37)](image)

**Figure 6.** Structures of (±)-torreyanic acid (36) and its analogue 37.

### 2.5. Nitrogen-Containing Heterocycles

Chaetoglobins A (38) and B (39) (Figure 7), the first azaphilone alkaloid dimers formed through bonding between C-5 and C-5′ [54], were isolated from a fungus, Chaetomium globosum, residing inside the stem of Imperata cylindrical by the Tan group [55,56]. Compound 38 has been demonstrated to be significantly cytotoxic against the human breast cancer cell line MCF-7 and colon cancer cell line SW1116 with IC<sub>50</sub> values of 42.1 and 55.7 μM, respectively. (−)-Alternarlactam (40, Figure 7), as a unique polyketide, was also described firstly by the Tan group and was obtained from a strain of Alternaria living inside the leaves of Carex aridula [57]. Compound 40 contains two important antitumor-related pharmacophores, cyclopentenone and isoquinolinone scaffolds, and was highly effective against human cervix HeLa adenocarcinoma cell and human hepatocellular carcinoma cell with IC<sub>50</sub> of 4.2 μM and 5.9 μM, respectively. The total synthesis of 40 has been achieved through using two commercially available chemicals, 3,5-dimethoxyaniline and (±)-4-methyl-1,2-cyclo-pentanediol [57].

The Gao group reported a polyketide-derived isoquinoline alkaloid, fusarimine (41, Figure 7) containing a rare N-ethyl-4-methyl-7-carboxyisoquinoline carbon skeleton [58]. This compound can be derived biogenetically from a single hexaketide chain with an external nitrogen incorporated in the endophytic fungus Fusarium sp. occurring in the renowned insecticidal plant Melia azedarach. Duclauxamid A1 (42, Figure 7) was purified from the endophytic Penicillium manginii inhabiting the elder root of the traditional Chinese medicinal (TCM) plant Panax notoginseng by the Huang group [59]. As a polyketide-derived heptacyclic oligophenalene dimer with an uncommon N-2-hydroxyethyl moiety [60], compound 42 demonstrated moderate cytotoxicity against HL-60, SMMC-7721, A-549, MCF-7, and SW480 cancer cell lines with IC<sub>50</sub> values ranging from 11 to 32 μM. From another TCM plant Camellia sinensis selected by Huang and co-workers, a bacterial endophyte, Streptomyces sp. was isolated and was found to produce a purple red solid, rubrolone B (43, Figure 7) with potential cardioprotection [61]. This metabolite belongs to the tropolone alkaloid family [62,63], but displays an expanded aromatic tropolone skeleton that includes a unique benzoic acid-pyridine inner salt fragment. Feeding experiments using <sup>13</sup>C-labeled acetates indicated a type-II polyketide synthase (PKS)-catalyzed biosynthesis route followed by complex oxidative rearrangements to form the tropolone ring system (Scheme 3) [61].
A novel ketal-tethered intramolecular Diels-Alder cycloaddition has been developed for the synthesis of compounds A (38) and B (39). It produced citreoviripyrone A (40) with an unprecedented carbon skeleton, was proposed to be derived from a PKS pathway similar to that of Alternaria alternata with MIC values of 3.9, 3.9, 7.8 and 1.95 μg/mL, respectively [68]. Compound 45 was toxic to human HCT 116 cells with a GI₅₀ value of 10.4 μM. Recently, Hertweck and co-workers reported a polyketide-derived antibiotic, daldionin (46), with an unprecedented oxane-linked binaphthyl ring system, obtained from an orchid endophyte [73]. Another endophytic fungus Cryptosporiopsis sp. isolated from tissues of Viburnum tinus proved to produce viburspiran (48). It was the first eight-membered maleic anhydride natural product with potential antifungal activity against Microbotryum violaceum and Botrytis cinerea with radii of inhibition zones of 6 and 10 mm at 50 μg per paper disk, respectively [74]. Chemical investigation of the EtOAc extract of the mangrove-derived system, obtained from an orchid endophyte [73]. Another endophytic fungus 

Figure 7. Structures of compounds 38–43.

Scheme 3. Biosynthesis of rubrolone B (43) on the basis of the data from feeding experiments.

2.6. Others

Following an antimicrobial screening for bioactive metabolites from endophytic fungi [64], fusidilactone C (44, Figure 8) was purified and found to comprise an unusual and rigid oxoadamantane skeleton and also has two ether-bridged hemiacetals in addition to its spiro acetal structure [65,66]. A novel ketal-tethered intramolecular Diels-Alder cycloaddition has been developed for the synthesis of the 2-oxadecalin spiroketal core of 44 [67]. Cephalosol (45, Figure 8), isolated from Cephalosporium acremonium that used to reside as an endophyte in Trachelospertum jasminoides, showed strong antimicrobial activities against Escherichia coli, Pseudomonas fluorescens, Trichophyton rubrum, and Candida albicans with MIC values of 3.9, 3.9, 7.8 and 1.95 μg/mL, respectively [68]. Compound 45, with an unprecedented carbon skeleton, was proposed to be derived from a PKS pathway similar to that of alternariol and graphislactones [69], and has already been a total synthesis target [70]. An endophytic fungus from the leaves of Catharanthus roseus was identified as Penicillium sp. by the Asai group [71]. It produced citreoviripyrone A (46, Figure 8) with a bicyclo[4.2.0]octadiene arising from a key 8π-6π electrocyclization cascade route (Scheme 4) [72]. Compound 46 was toxic to human HCT 116 cells with a GI₅₀ value of 10.4 μM. Recently, Hertweck and co-workers reported a polyketide-derived antibiotic, daldionin (47, Figure 8) with an unprecedented oxane-linked binaphthyl ring system, obtained from an orchid endophyte [73]. Another endophytic fungus Cryptosporiopsis sp. isolated from tissues of Viburnum tinus proved to produce viburspiran (48, Figure 8) [74]. It was the first eight-membered maleic anhydride natural product with potential antifungal activity against Microbotryum violaceum and Botrytis cinerea with radii of inhibition zones of 6 and 10 mm at 50 μg per paper disk, respectively [74]. Chemical investigation of the EtOAc extract of the mangrove-derived...
endophyte Corynespora cassiicola isolated from Laguncularia racemosa, provided five unusual octalactone derivatives, such as coryoctalactone E (49, Figure 8) [75].

![Structures of compounds 44–49](image)

Figure 8. Structures of compounds 44–49.

![Scheme 4](image)

Scheme 4. Plausible biosynthetic pathway of citreoviripyrene A (46).

Citrinals A and B (50 and 51, Figure 9) from the endophytic fungus Colletotrichum capsici represented a new compound class with a unique skeleton but displayed no cytotoxic activities [76,77]. Following a biochemical induction assay, cytoskyrins A and B (52 and 53, Figure 9) with a 1,3,6,8-tetrahydroxyanthraquinone-type carbon skeleton, were isolated from the endophytic fungus Cytospora sp. [78]. Compound 52 demonstrated strong biochemical induction assay (BIA; used to identify compounds that damage DNA or inhibit DNA synthesis) activity down to 12.5 ng while the biosynthetically related 53 was inactive. The total synthesis has already been reported by the group of Nicolaou by developing a cascade sequence called the “cytoskyrin cascade” [79–81].
3. Noribosomal Peptides

Aspertryptanthrins A–C (54–56, Figure 10), three new indole diketopiperazine alkaloids, were obtained from a strain of *Aspergillus* sp. isolated from the stem bark of *Melia azedarach* L. [82].

They possess a 6/5/6/6 tryptanthrin framework that is formed by a tryptophan unit and an anthranilate residue. In addition, compound 56 has an unusual 16-membered ring skeleton which was cyclized through the formation of phenylate. Spirobrocazines A and B (57 and 58, Figure 10)
were isolated and identified from the mangrove-derived *Penicillium brocae* and possess a very rare spirocyclic skeleton [83]. Compound 57 showed moderate antibacterial activities against *E. coli*, *S. aureus*, and *Vibrio harveyi* with MIC values of 32.0, 16.0, and 64.0 μg/mL, respectively.

Neosartoryadins A (59) and B (60) (Figure 11) with a unique 6/6/6/5 quinazoline ring system connected directly to a 6/5/5 imidazoindolone ring system, represented a new class of quinazoline-containing indole alkaloids and displayed inhibitory effects against influenza A virus (H1N1) with IC<sub>50</sub> values of 66 μM and 58 μM, respectively [84]. Their structures were proposed to be assembled by four amino acids L-tryptophan, anthranilic acid (ATA), L-valine, and 2-aminoisobutyric acid (Aib) in the endophytic fungus *Neosartorya udagawae* [84,85].

Antitumor screening of extracts of 43 endophytic fungi isolated from the leaves of the TCM plant *Adenophora axilliflora* enabled the discovery of a bioactive strain, *Chaetomium* sp. [86]. 1H-NMR and bioassay fractionation of the fungal culture led to the isolation of a tripeptide-derived alkaloidal metabolite, chaetominine (61, Figure 11) with a unique alanine-derived δ-lactam ring [87]. Compound 61 showed more potent cytotoxicity to the human leukemia K562 and colon cancer SW1116 cell lines than the positive drug 5-fluorouracil (IC<sub>50</sub> values of 21.0 and 28.0 nM for compound 61), respectively; IC<sub>50</sub> values of 33.0 and 76.0 nM for 5-fluorouracil, respectively) [86]. It was proposed to be biosynthesized from L-alanine, ATA, and D-tryptophan and has been a target for numerous synthetic efforts [88]. Apicidins A–C (62–64, Figure 11), three new members of a unique family of cyclic tetrapeptides, were isolated from a fungal endophyte *Fusarium pallidoroseum* by chemists from Merck research laboratories [89,90]. They showed a variety of potent antiprotozoal activities by reversibly inhibiting histone deacetylase (HDAC) and are attracting considerable attention for their anti-tumor effects [91–93]. In particular, compound 64 showed MIC values of 0.8, 101, and 69 nM against *Besnoitia jellisoni*, *Eimeria tenella*, and *Plasmodium falciparum*, respectively, and was slightly more active than compounds 62 and 63 [90].

![Structures of compounds 59–64.](image)

**Figure 11.** Structures of compounds 59–64.

4. **Isoprenoids**

4.1. **Steroids**

Solanioic acid (65, Figure 12), a degraded and rearranged steroid with an unprecedented carbon skeleton, has been isolated from the fungus *Rhizoctonia solani* obtained from tubers of the
medicinal plant *Cyperus rotundus* [94]. It displayed significant inhibitory activities against *B. subtilis, S. aureus*, and methicillin-resistant *S. aureus* (MRSA) with MIC values around 1 µg/mL, and moderate antifungal activity against *C. albicans* with an MIC value of 16 µg/mL [94]. Asterogynins A (66) and B (67) (Figure 12), two unusual steroid-like metabolites with a tetracyclic carbocyclic ring system [95], were purified from the culture of *Chalara alabamensis* isolated from the host plant *Asterogyne martiana* [96]. More recently, four structurally related steroids, wortmannines A–C (68–70, Figure 12) and secovironolide (71, Figure 12) bearing an unusual five-membered B ring [97,98], were discovered from an endophytic fungus *Talaromyces wortmannii* living in *Tripterygium wilfordii* by the group of Yang.

Figure 12. Structures of compounds 65–71.

### 4.2. Sesquiterpenoids

Chloropupukeanannin (72, Figure 13) featuring a unique tricyclo-[4.3.1.03,7]-decane skeleton, was the first chlorinated pupukeannane derivative originated from a sesquiterpenoid in the plant endophyte *Pestalotiopsis fici* [99,100]. It inhibited the HIV-1 replication in C8166 cells at an IC₅₀ of 14.6 µM and also exhibited weak antibacterial activity [100]. A key intermolecular Diels-Alder reaction followed by a subsequent carbonyl-ene reaction was proposed to be involved in the biosynthesis of compound 72 [100,101]. More novel pupukeannane derivatives with significant anti-HIV or anticancer activities, such as chloropestolide A (73) [102] and chloropupukeanolides A–E (74–78, Figure 13) [103,104], have also been reported from endophytes. Compounds 73 and 74 showed inhibitory effects on replication of the HIV-1 virus in C8166 cells with IC₅₀ values of 62.4 and 6.9 µM, respectively, and inhibited the growth of HeLa cell line with IC₅₀ values of 0.7 and 16.9 µM, respectively [102,103]. Compounds 76 and 77 demonstrated significant cytotoxicity against HeLa and HT29 cell lines with IC₅₀ values ranging from 1.2 to 7.9 µM [104].

Periconianone A (79, Figure 13), the first member of sesquiterpenoids with a new 6/6/6 tricarbocyclic skeleton, was isolated from *Periconia sp.* derived from the medicinal plant *Annona muricata* [105]. An intramolecular aldol condensation for the formation of a carbon bond between C-4 and C-12 might result in the generation of the unusual six-membered carbonic ring, which has recently been utilized in the totally synthetic strategy to 79 (Scheme 5) [106].
Figure 13. Structures of compounds 72–83.

Scheme 5. (A) Proposed biosynthetic pathway for periconianone A (79); (B) Synthetic strategy to 79 inspired by the biogenetic hypothesis of 79.
Compound 79 exhibited significant neural anti-inflammatory activity against lipopolysaccharide (LPS)-induced NO production in mouse microglia BV2 cells with IC$_{50}$ value of 0.15 μM (curcumin as a positive control, IC$_{50}$ = 3.9 μM) [105]. Pestalotiopsin A (80, Figure 13), an immunosuppressive agent, was isolated from an endophytic fungus Pestalotiopsis sp. associated with Taxus brevifolia by the group of Clardy [107]. The oxatricyclic ring system in the sesquiterpenoid 80 is unprecedented among natural products. In 2015, Ding et al. isolated three plant-like sesquiterpenes, bacarylanes A–C (81–83, Figure 13) from a mangrove-derived bacterial endophyte Streptomyces sp. [108]. They were identified as the mirror images of plant-derived caryolanes [109]. This discovery may point to complex cross-talk between plant and endophytic microorganisms [20].

4.3. Diterpenoids

From an unidentified fungus colonizing the plant Daphnopsis americana, guanacastepene A (84, Figure 14) and 14 biosynthetically related congeners that comprised a unique family of diterpene natural products were found [110,111]. Compound 84 showed potent antibacterial activity against MRSA and vancomycin-resistant Enterococcus faecalis (VREF) through disrupting the cell membrane with inhibition zones of 11 and 9 mm at 100 μg per paper disk, respectively [111,112]. It has attracted numerous synthetic efforts or strategies toward the guanacastepenes [113,114]. Harziandione (85, Figure 14) and harzianone (86, Figure 14) are antimicrobial harziane diterpenes containing a unique tetracyclic scaffold from the potential biocontrol agents, Trichoderma spp. [115].

![Figure 14. Structures of diterpenoids 84–86.](image)

4.4. Sesterterpenoids

The group of She has been dedicated to the search for structurally unique and biologically active compounds from mangrove plant-derived fungal endophytes, especially Aspergillus spp. Five sesterterpenoids with an unprecedented carbon skeleton including asperterpenoid A (87), asperterpenols A and B (88 and 89), and aspterpenacids A and B (90 and 91), have been obtained (Figure 15) [116–118]. Among them, compound 87 with an unprecedented 5/7/(3)6/5 pentacyclic system, inhibited the Mycobacterium tuberculosis protein tyrosine phosphatase B with an IC$_{50}$ value of 2.2 μM [116]. Compounds 88 and 89 possessing an unusual 5/8/6/6 tetracyclic ring skeleton, exhibited inhibitory activity against acetylcholinesterase (AChE) with IC$_{50}$ values of 2.3 μM and 3.0 μM, respectively [118]. There were no antibacterial and cytotoxic activities for compounds 90 and 91 with a rare carbon skeleton of a 5/3/7/6/5 ring system [117].

![Figure 15. Structures of sesterterpenoids 87–91.](image)
5. Hybrid Products

5.1. PKS-NRPS

Cytochalasans are a large class of fungal secondary metabolites with biological diversity originating from a mixed PKS and nonribosomal peptide synthetase (NRPS) [119]. The group of Dai isolated an endophytic fungus Periconia sp. from the medicinal plant Annona muricata, and discovered it was cytotoxic to several human cancer cell lines. Bioassay-guided isolation of EtOAc extracts of the different fermentation media of this strain resulted in the isolation and identification of twelve novel PKS-NRPS hybrid cytochalasans [120–124]. Among them, periconiasins A and B (92 and 93, Figure 16) with an unprecedented 9/6/5 tricyclic ring system exhibited significant cytotoxicity against human HCT-8 cancer cells with IC₅₀ values of 0.9 and 0.8 µM, respectively [123]. Periconiasin D (94, Figure 16) has a 5/6/6/5 tetracyclic ring skeleton, while periconiasin G (95, Figure 16) is the first cytotoxic cytochalasan with a 7/6/5 tricyclic ring system [120]. Pericoannosin A (96, Figure 16) possesses an unusual hexahydro-1H-isochromen-5-isobutylpyrrolidin-2-one skeleton and showed moderate anti-HIV activity (IC₅₀ of 69.6 µM) [122,124]. Compounds 92–96 were proposed to be biosynthesized from an unusual seven acetate/malonate polyketide chain attached to a leucine unit by a PKS-NRPS and a key Diels-Alder reaction should be occurred in the cyclization of cytochalasans [122,123]. Owing to their structural diversity and biological activities, they have emerged as targets for bioinspired total syntheses [125].

From a fungal endophyte Trichoderma gamsii isolated from the traditional Chinese herb Panax notoginseng, three more unique cytochalasans, trichoderones A (97) and B (98) (Figure 16) together with trichodernone (99, Figure 16), were obtained by Zou and co-workers [126,127]. Their structures with an unprecedented pentacyclic or tetracyclic ring system might originate from a key intramolecular Michael 1,4-addition of the possible biosynthetic precursor aspochalasin D [126,127]. Compounds 97 and 98 showed weak inhibitory activity against the HeLa cell lines with IC₅₀ values over 40 µM [127]. Recently, phomochalasins A (100) and B (101) (Figure 17), two novel cytochalasans featuring unprecedented 5/6/5/8-fused tetracyclic or 5/6/6/7/5-fused pentacyclic skeletons, were isolated from the endophytic fungus Phomopsis sp., and compound 101 showed antimigratory activity against MDA-MB-231 with IC₅₀ value of 19.1 µM [128].

![Figure 16. Structures of compounds 92–99.](image_url)

Chemical investigation of a mangrove-derived endophytic fungus Campylocarpon sp., led to the isolation of four novel cytotoxic 4-hydroxy-2-pyridone alkaloids, campyridones A–D (102–105, Figure 17) [129]. Their unprecedented ring systems containing a spiro-furanone or γ-pyrone substructure were proposed to be synthesized by the PKS-NRPS hybrid involving a polyketide chain and a tyrosine moiety.
Clardy and co-workers reported the isolation of two hybrid PKS-NRPS products: phaeosphaeride A (106, Figure 18) and its inactive diastereomer phaeosphaeride B (107, Figure 18) from an endophytic fungus *Phaeosphaeria avenaria* [130]. They were potent inhibitors of signal transducer and activator of transcription 3 (STAT3) signaling with an IC$_{50}$ of 0.61 mM [130]. Their structural elucidations were achieved by spectral data [130], total synthesis [131,132] and X-ray crystallographic analysis [133]. The diastereomers or semi-synthetic derivatives of compounds 106 and 107 exhibited in vitro cytotoxicity against MD-MB-231, PANC-1, and A549 cancer cell lines [134,135]. Another biosynthetically related hybrid PKS-NRPS product, paraphaeosphaeride A (108, Figure 18), was discovered from an endophytic *Paraphaeosphaeria neglecta* isolated from the stem of Hawaiian-plant *Lycopodiella cernua* [136]. It has an unusual 4-pyranone-$\gamma$-lactam-1,4-thiazine moiety and showed STAT3 inhibition at 10 $\mu$M. The plausible hybrid biosynthetic pathway of compound 108 involving a precursor cysteine has been shown in Scheme 6 [136,137].
A proline-pentaketide amide, penibrugieramine A (109, Figure 18) with an unprecedented 1-hydroxy-2-methylpyrrolizidin-3-one skeleton, was isolated from *Penicillium* sp. associated with the Chinese mangrove *Bruguiera gymnorrhiza* [138]. A biomimetic total synthesis of compound 109 involving a key intramolecular aldol-type reaction was accomplished by Kim et al. [139]. The endophytic fungus *Cryptosporiopsis cf. quercina* produced a unique functionalized tetramic acid, cryptocin (110) (Figure 18) arising from a mixed PKS-NRPS pathway [140,141]. It demonstrated significant inhibitory activity against a wide variety of plant pathogens, including the fungus *Pyricularia oryzae* (the causal agent of rice blast disease) with an MIC value of 0.39 µg/mL [140]. Further total synthesis, semi-synthetic and biological studies by the group of Gao suggested the importance of different tetramic acid ring systems for cytotoxicity [142]. A high-throughput screen for endophytes-derived antimalarial compounds enabled the discovery of a new tryptophan-polyketide hybrid with a polyketide decalin [141], codinaeopsin (111, Figure 18) [143]. Compound 111 had an IC$_{50}$ of 4.66 µM against *P. falciparum*, the causative agent of the most lethal form of malaria.

### 5.2. NRPS-Terpenes

A mangrove-derived endophyte *Mucor irregularis* was found to produce three novel indole-diterpenes [144], named rhizovarins A–C (112–114, Figure 19) [145]. They appeared to be chemically unique due to the complex 4,6,6,8,5,6,6,6,6-fused indole-diterpene ring system that incorporates an unusual acetal linked to a hemiketal (112) or a ketal (113 and 114). Compounds 112 and 113 were effective against the human A-549 (IC$_{50}$: 11.5 µM for 112; 6.3 µM for 113) and HL-60 cancer cell lines (IC$_{50}$: 9.6 µM for 112; 5.0 µM for 113) [145].

The group of Ji isolated and identified a novel prenylated indole alkaloid, aspeverin (115, Figure 19) from an endophytic strain *Aspergillus versicolor* harbored in the marine green alga *Codium fragile* [146]. It showed inhibitory activity against marine phytoplankton (*Heterosigma akashiwo*) with the EC$_{50}$ values of 16.7 and 9.0 µM for 24 and 96 h, respectively. The structure of compound 115 containing an unprecedented cyclic carbamate linkage and a rare cyano could be assembled through a dipeptide-like precursor with dimethylallyl pyrophosphate (DMAPP) [147,148], and has promoted the attention of chemists from a totally synthetic perspective [149]. Varioxepine A (116, Figure 19), a 3H-oxepine-containing alkaloid with an unprecedented oxa-cage unit, was isolated from *Paecilomyces variotii*, an endophytic fungus residing in marine red alga [150]. It showed diverse antibacterial activities with MIC values ranging from 16 to 64 µg/mL and inhibited plant pathogenic fungus *Fusarium graminearum* with an MIC value of 4 µg/mL. Like compounds 59–60, compound 116 could be biosynthesized by the condensation of ATA, valine, phenylalanine, and DMAPP [151].
5.3. PKS-Terpene

Two novel hybrid sesquiterpene-cyclopaldic acid metabolites, named pestalotiopens A (117) and B (118) (Figure 20), were obtained from the marine endophytic fungus *Pestalotiopsis* sp. [152]. Compound 117 showed moderate antibacterial activity against *E. faecalis* whereas compound 118 containing a third, triketide-derived moiety was inactive. Three unusual polyketide-sesquiterpene metabolites peyronellins A–C (119–121, Figure 20), have been isolated from the endophytic fungus *Peyronellaea coffeae-arabicae*, which was isolated from the native Hawaiian plant *Pritchardia lowreyana* [153]. Compound 119 was active against A2780 and A2780 CisR cancer cell lines with IC$_{50}$ values of 1.8 and 3.4 µM, respectively, while compounds 120 and 121 were inactive.

![Figure 19. Structures of compounds 112–116.](image)

![Figure 20. Structures of pestalotiopens A–B (117–118) and peyronellins A–C (119–121).](image)
5.4. PKS-NRPS-Terpene

From a plant endophytic fungus *Emericella nidulans*, emericellolides A–C (122–124, Figure 21) with an unprecedented macrolide skeleton were found by Li and co-workers. A L-glutamate fragment, an isoindolone unit [154], and a sesquiterpene moiety might be involved in the construction of the macro-ring in compounds 122–124 [155].

![Structures of emericellolides A–C](image1)

Emericellolide A (122)  Emericellolide B (123) \( \text{R} = \text{OMe} \)  Emericellolide C (124) \( \text{R} = \text{OH} \)

Figure 21. Structures of emericellolides A–C (122–124).

An endophytic fungus *Aspergillus versicolor* was isolated from the rhizome of *Paris polyphylla* var. *yunnanensis* by Zhou et al. and was found to biosynthesize five highly oxygenated cyclopiazonic acid-derived alkaloids, aspergillines A–E (125–129, Figure 22) [156,157]. Compounds 125–129 with a rigid hexacyclic (6/5/6/5/5/5) indole-tetrahydro-furan-tetramic acid scaffold, were proposed to arise from a mixed biosynthetic pathway that involves a tryptophan unit, one or two molecules of acetate, and DMAPP [158–160]. They not only exhibited significant anti-tobacco mosaic virus (anti-TMV) activity with IC\(_{50}\) values of 15.4–48.6 \( \mu \text{M} \), but also showed moderate cytotoxicity against a panel of human cancer cell lines [157].

![Structures of aspergillines A–E](image2)

Aspergilline A (125)  Aspergilline B (125)  Aspergilline C (127)  Aspergilline D (128)  Aspergilline E (129)

Figure 22. Structures of aspergillines A–E (125–129).

6. Conclusions

Stereochemically complex and structurally diverse secondary metabolites play a pivotal role in discovery campaigns for new natural product drug pharmacophores. A number of structurally novel
compounds are increasingly being discovered from endophytic fungi and bacteria and could comprise a powerful compound library for drug lead development. Herein, we present a comprehensive review of 129 endophyte-derived natural products with new carbon skeletons, unusual ring systems, or rare structural moieties (Table 1). Most of them were discovered from fungal endophytes in which more than 70% were isolated from terrestrial plants, especially those with an ethnobotanical history. The structural novelty and diversity of these microbial metabolites are as a result of the enormous diversity of terrestrial and marine endophytes in combination with their potential biosynthetic capabilities. In addition, they display diverse and remarkable biological activities, and frequently reported biological properties are antimicrobial and cytotoxic activities (Table 1). As shown in Figure 23, 16 secondary metabolites with marked biological activities might deserve more attention from chemists and biologists in further investigations.

**Figure 23.** Selected endophyte-derived secondary metabolites with significant biological activities.
Table 1. Structurally novel natural products from endophytic bacteria or fungi.

| Microorganisms | Origin | Secondary Metabolites (Figures) | Reported Activities* | Ref. |
|----------------|--------|---------------------------------|----------------------|------|
| Streptomyces sp. | Marine, Brugiaena gymnorrhiza | Divergolides A–D (1–4) (Figure 1) | Antibacterial, cytotoxicity | [28] |
| Streptomyces sp. | Terrestrial, Camelina sinensis | Rubrolone B (43) (Figure 7) | NR | [61] |
| Streptomyces sp. | Marine, Brugiaena gymnorrhiza | Bacaryloolides A–C (81–83) (Figure 13) | NR | [108] |
| Chalaraspora | Terrestrial, Arthromycetes vulgaris | Isofusidienol A–D (22–25) (Figure 4) | Antibacterial | [39] |
| A nonsporulating fungus | Terrestrial, Knightia excelsa | Spiro-mamakone A (32) (Figure 5) | Antibacterial, cytotoxicity | [45] |
| Penicillium brocae | Marine | Spirobrocine A–B (57–58) (Figure 10) | Antibacterial, cytotoxicity | [83] |
| Pestalotiopsis fici | Terrestrial | Chloropupukeananin (72) (Figure 13) | Antibacterial, antiviral | [100] |
| Unidentified fungus | Terrestrial, Daphnopsis americana | Guanacastepene A (84) (Figure 14) | Antibacterial | [110,111] |
| Brelinora sp. | Terrestrial, Carpobrotus edulis | Bellenolides A–G (11–17) (Figure 3) | Antifungal, antialgal | [36] |
| Cryptosporiopsis sp. | Terrestrial, Viburnum tinus | Viburspiran (48) (Figure 8) | Antifungal | [74] |
| Cephalosporium acrimonion | Terrestrial, Tripterygium wilfordii | Cryptocin (110) (Figure 18) | Antifungal | [146] |
| Daldinia echscholtzii | Terrestrial, Pachyphallus oxyl | Daldilone (47) (Figure 9) | Antimicrobial | [68] |
| Neosartorya adageaueae | Terrestrial, Cyperus rotundus | Solanoic acid (65) (Figure 12) | Antimicrobial | [73] |
| Trichoderma spp. | Marine, alga Codium fragile | Harziandione (85) and harzianone (86) (Figure 14) | Antimicrobial | [115] |
| Paeollomyces variotii | Marine, Rhizophasia mucronata | Varioexine A (116) (Figure 19) | Antimicrobial | [150] |
| Pestalotiopsis fici | Terrestrial | Pestalotipensiens A–B (117–118) (Figure 20) | Antimicrobial | [152] |
| Periconia sp. | Terrestrial, Annona muricata | Periconosin A (96) (Figure 16) | Anti-HIV | [122] |
| Neosartorya adageaueae | Marine, Arioconia marina | Neosartoryadin A–B (59–60) (Figure 11) | Antiviral | [84] |
| Aspergillus versicolor | Terrestrial, polychryla var. guanenensis | Aspergilinosine A–E (125–129) (Figure 22) | Antiviral, cytotoxicity | [157] |
| Periconia sp. | Terrestrial, Annona muricata | Periconianone A (79) (Figure 13) | Anti-inflammatory | [105] |
| Unidentified genus | Terrestrial, Vochysia guatemalensis | Codinaceospin (111) (Figure 18) | Antimarial | [143] |
| Phomopsis sp. | Terrestrial, Isodon ericoides var. laxiflora | Phomolphasalin A–B (100–101) (Figure 17) | Antimicrobial activity | [128] |
| Fusarium pallidumense | Terrestrial | Apicinides A–C (62–64) (Figure 11) | Antiprotozoal, anticancer | [90] |
| Aspergillus fuscus | Terrestrial, Ophiocordus frutescens | Actinonolides E–F (5–9) (Figure 2) | Anti-trypanosomal | [34] |
| Aspergillus sp. | Marine, Archeconia marina | Asperterpenoid A (87) (Figure 15) | Antituberculosis | [116] |
| Aspergillus sp. | Marine | Asperterpenoid A–B (88–89) (Figure 15) | Acetylcholinesterase inhibition | [118] |
| Cytospora sp. | Terrestrial, Conocarpus erecta | Cytoskyrin A–B (52–53) (Figure 9) | BIA activity | [78] |
| Unidentified genus | Terrestrial, Ficus microcarpa L. | Microcarpalide (10) (Figure 2) | Cytotoxicity | [35] |
| Nodulisporiun sp. | Marine, Alga | Noduliprenovone (18) (Figure 3) | Cytotoxicity | [37] |
| Pestalotiopsis virgata | Terrestrial, Dracoumumon dumrerum | Virgatolide A–C (27–29) (Figure 5) | Cytotoxicity | [41] |
| Pestalotiopsis microspora | Terrestrial, Toxopha taxifolia | (±)-torreyanian acid (36) (Figure 6) | Cytotoxicity | [50] |
Table 1. Cont.

| Microorganisms | Origin | Secondary Metabolites (Figures) | Reported Activities | Ref. |
|----------------|--------|---------------------------------|--------------------|------|
| Chaetomium globosum | Terrestrial, Imperata cylindrica | Chaetoglobins A–B (38–39) (Figure 7) | Cytotoxicity | [56] |
| Alternaria sp. | Terrestrial, Carex aridula | (-)-Alternarlactam (40) (Figure 7) | Cytotoxicity | [57] |
| Penicillium manginii | Terrestrial, Panax notoginseng | Duclauxamide A1 (42) (Figure 7) | Cytotoxicity | [59] |
| Penicillium sp. | Terrestrial, Catharanthus roseus | Citreoviripyrone A (46) (Figure 8) | Cytotoxicity | [71] |
| Chaetomium sp. | Terrestrial, Adenophora axilliflora | Chaetominine (61) (Figure 11) | Cytotoxicity | [86] |
| Pestalotiopsis fici | Terrestrial | Chloropupukeanolides A–E (74–78) (Figure 13) | Cytotoxicity | [103,104] |
| Trichoderma gamsii | Terrestrial, Panax notoginseng | Trichoderones A–B (97–98) (Figure 16) | Cytotoxicity | [127] |
| Trichoderma gamsii | Terrestrial, Panax notoginseng | Trichodermone (99) (Figure 16) | Cytotoxicity | [126] |
| Campylocarpon sp. | Marine, Sonneratia caseolaris | Campyridosine A–D (102–105) (Figure 17) | Cytotoxicity | [129] |
| Mucor irregularis | Marine, Rhizopora stylosa | Rhizovarins A–C (112–114) (Figure 19) | Cytotoxicity | [145] |
| Campylocarpon sp. | Terrestrial, Pritchardia lowreyana | Peyronellins A–C (119–121) (Figure 20) | Cytotoxicity | [153] |
| Pestalotiopsis sp. | Terrestrial, Taxus brevifolia | Pestalotiopsis A (80) (Figure 13) | Inhibitors of the release of β-glucuronidase | [107] |
| Penicillium dangeardii | Terrestrial, Lysidice rhodostegia | Penicillactones A–C (33–35) (Figure 5) | Penicillactones A–C (33–35) (Figure 5) | Inhibiting STAT3 activity | [130] |
| Phaeosphaeria avenaria | Terrestrial | Phaeosphaeride A–B (106–107) (Figure 18) | Penicillactones A–C (33–35) (Figure 5) | Inhibiting STAT3 activity | [130] |
| Aspergillus versicolor | Marine, green alga Codium fragile | Asperverin (115) (Figure 19) | Penicillactones A–C (33–35) (Figure 5) | Inhibiting STAT3 activity | [130] |
| Microphaeopus sp. | Terrestrial, Lycium intricatum | Microphaeopsones A–C (19–21) (Figure 4) | Penicillactones A–C (33–35) (Figure 5) | Inhibiting STAT3 activity | [130] |
| Paraphaeosphaeria neglecta | Terrestrial, Lycopodiella cernua | Lycopodiellactone (26) (Figure 4) | Penicillactones A–C (33–35) (Figure 5) | Inhibiting STAT3 activity | [130] |
| Pestalotiopsis virgata | Terrestrial, Terminalia chebula | Pestalospiranes A–B (30–31) (Figure 5) | Penicillactones A–C (33–35) (Figure 5) | Inhibiting STAT3 activity | [130] |
| Pestalotiopsis sp. | Terrestrial, Clavaria stds. | Torreyanic acid analogue (37) (Figure 6) | Penicillactones A–C (33–35) (Figure 5) | Inhibiting STAT3 activity | [130] |
| Fusarium sp. | Terrestrial, Melia azedarach | Fusarimine (41) (Figure 7) | Penicillactones A–C (33–35) (Figure 5) | Inhibiting STAT3 activity | [130] |
| Fusidium sp. | Terrestrial, Mentha arvensis | Fusidilactone C (44) (Figure 8) | Penicillactones A–C (33–35) (Figure 5) | Inhibiting STAT3 activity | [130] |
| Corynespora cassiicola | Marine, Laguncularia racemosa | Coryoctalactone E (49) (Figure 8) | Penicillactones A–C (33–35) (Figure 5) | Inhibiting STAT3 activity | [130] |
| Colletotrichum capsici | Terrestrial, Sagesbeckia pubescens | Citrinals A–B (50–51) (Figure 9) | Penicillactones A–C (33–35) (Figure 5) | Inhibiting STAT3 activity | [130] |
| Aspergillus sp. | Terrestrial, Melia azedarach L. | Aspertryptanthrins A–C (54–56) (Figure 10) | Penicillactones A–C (33–35) (Figure 5) | Inhibiting STAT3 activity | [130] |
| Chalara alabamensis | Terrestrial, Asterosygea martiana | Asterosygenins A–B (66–67) (Figure 12) | Penicillactones A–C (33–35) (Figure 5) | Inhibiting STAT3 activity | [130] |
| Talaromyces wortmannii | Terrestrial, Trichromyces wilfordii | Wortmanninos A–C (68–70) (Figure 12) | Penicillactones A–C (33–35) (Figure 5) | Inhibiting STAT3 activity | [130] |
| Talaromyces asperti | Terrestrial, Trichogyton wilfordii | Secovironolide (71) (Figure 12) | Penicillactones A–C (33–35) (Figure 5) | Inhibiting STAT3 activity | [130] |
| Aspergillus sp. | Marine, Kandelia obovata | Asperpenacids A–B (90–91) (Figure 15) | Penicillactones A–C (33–35) (Figure 5) | Inhibiting STAT3 activity | [130] |
| Paraphaeosphaeria neglecta | Terrestrial, Lycopodiella cernua | Paraphaeosphaeride A (108) (Figure 18) | Penicillactones A–C (33–35) (Figure 5) | Inhibiting STAT3 activity | [130] |
| Penicillium sp. | Marine, Bruguiera gymnorrhiza | Penibruguieramine A (109) (Figure 18) | Penicillactones A–C (33–35) (Figure 5) | Inhibiting STAT3 activity | [130] |
| Emericella nidulans | Terrestrial, Tamarix chinensis Lour | Emericellolides A–C (122–124) (Figure 21) | Penicillactones A–C (33–35) (Figure 5) | Inhibiting STAT3 activity | [130] |

* Organize the bioactivity using alphabetical order. b NR: not reported in references or have reported in literature to have no biological activities.
Although traditional bioassay-guided chemical investigation encounters the frequent re-isolation of known compounds, it remains the most popular approach in discovering structurally novel small molecules from endophytes, especially with the aid of advanced analytical techniques, such as LC-MS. Alteration of easily accessible cultivation parameters, such as media composition, has well proven in this review to activate the silent gene clusters in endophytes and will continue to be used as a promising strategy for increasing the number of novel natural products by a single microbial strain.

Furthermore, recent advances in microbial genomics and metagenomics offer promising opportunities to access cryptic secondary metabolites. It is expected that most endophytic species are more likely to be uncultivable or poorly cultivable in standard laboratory conditions. Exploration of this largely unexplored source would provide more structurally unique compounds with properties suitable for a wide variety of biological and medicinal applications.

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