



Review

Endophytic Fungal Terpenoids: Natural Role and Bioactivities

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Abstract: Endophytic fungi are a highly diverse group of fungi that intermittently colonize all plants without causing symptoms of the disease. They sense and respond to physiological and environmental changes of their host plant and microbiome. The inter-organism interactions are largely driven by chemical networks mediated by specialized metabolites. The balance of these complex interactions leads to healthy and strong host plants. Endophytic strains have particular machinery to produce a plethora of secondary metabolites with a variety of bioactivities and unknown functions in an ecological niche. Terpenoids play a key role in endophytism and represent an important source of bioactive molecules for human health and agriculture. In this review, we describe the role of endophytic fungi in plant health, fungal terpenoids in multiple interactions, and bioactive fungal terpenoids recently reported from endophytes, mainly from plants used in traditional medicine, as well as from algae and mangroves. Additionally, we highlight endophytic fungi as producers of important chemotherapeutic terpenoids, initially discovered in plants. Despite advances in understanding endophytism, we still have much to learn in this field. The study of the role, the evolution of interactions of endophytic fungi and their terpenoids provide an opportunity for better applications in human health and agriculture.



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1. Introduction

Endophytic fungi are a phylogenetically diverse group of fungi that asymptotically and intermittently colonize plant tissue, driving saprophytic, commensalistic or mutualistic interaction with their host plant [1,2]. We can divide endophytic fungi into two groups: (1) Clavicipitaceous, represented by the genera *Epichloë* and *Neotyphodium*, and distinguished by a tight range of hosts and by mainly being transmitted vertically; (2) Nonclavicipitaceous, composed of a vast number of genera of Ascomycota, Mucormycota, and Basidiomycota [3]. The most commonly isolated genera include *Penicillium*, *Alternaria*, *Fusarium*, *Colletotrichum*, *Aspergillus*, and *Xylaria* [4]; nevertheless, the frequency of isolation depends on the plant species and genotypes, plant tissue samples, the geography of the plant, and the season of sampling [5–8]. Furthermore, endophytic strains are different from those that are non-endophytic given their different evolutionary and ecological context [5].

The endophytic fungal association is a complex chemical interkingdom interaction that involves the modulation of the defense mechanisms of the host plant and the regulation of fungal virulence factors, as well as antagonistic and cooperative interactions with other members of the microbiome [9]. A delicate balance between host plants with endophytic fungi and the rest of the microbiome leads to healthy plants [10]; moreover, endophytic fungi help to maintain plant health even under biotic and abiotic stress conditions [11,12]. As a consequence of these interactions, endophytic fungi produce a variety of secondary metabolites that can be exploited biotechnologically [11].

Terpenoids are the largest and diverse group of bioactive secondary metabolites. They perform important ecological functions, as defense and signaling molecules [13]. Endophytes biosynthesize a structurally and functionally diverse portfolio of terpenoids that act as long-distance communication among fungi and bacteria, insect attractors, antagonistic chemicals, plant growth promoters, or signaling molecules during symbiosis interaction [14]. Additionally, terpenoids are utilized as therapeutic drugs in human health. Indeed, remarkable drugs such paclitaxel, camptothecin, *Vinca alkaloids*, as well as fusidic acid, are natural terpenoid products [15]. Hundreds of new bioactive terpenoids have been isolated and characterized from endophytic fungi from sources such as plants used in traditional medicine, crops, algae, and mangroves [16].

Despite hundreds of publications on endophytic fungi that unquestionably place them as valuable sources of novel and known bioactive terpenoids, as well as recent advances in technology, fundamental questions remain unanswered in aspects such as plant–endophyte coevolution, horizontal gene transfer, metabolic pathways, and mechanisms underlying global interaction among endospheric and rhizospheric organisms. Therefore, integral studies, considering organisms at all levels and their interactions along with environmental aspects, have become indispensable.

2. Fungi Living Inside Plants

Initially, the term endophyte was used by De Bary, in 1866, to refer to all organisms that live within plant tissues [17]. During the study of endophytic tree leaf fungi, the term was defined to refer to fungi that live inside plants at some point in their life and that can colonize the internal tissues of plants without causing apparent damage, including latent pathogens that can live asymptotically in their host for some time [18]. As the use of the term became popular and knowledge about these organisms increased, confusion and ambiguities arose in this regard [19]. In 1995, Wilson cleared up some confusion and misuse of the term. In this way, he highlighted that endophytic fungi colonize plant tissues without producing disease symptoms, defining them in terms of the nature of the plant–endophyte association [20]. Therefore, endophytic fungi include the entire spectrum of symbiotic interactions between plants and fungi: parasitism, commensalism, and mutualism [21]. Currently, we can highlight three characteristics of endophytes in terms of colonization of the plant: (1) they colonize the plant discreetly and for a long time; (2) colonization ceases temporarily; and (3) then, colonization resumes because of physical changes or modulators of the host plant. Whether the endophyte is subsequently considered a latent pathogen, a saprophyte, or a mutualist, episodic growth is a defining feature of endophytism [2]. To these characteristics, we can add that endophytic fungi have been found in all the main lineages of terrestrial plants, forming small ecosystems within them, and endophytic fungi strains are genetically different from pathogenic strains [1].

3. Endophytic Fungal Communities Are Diverse and Context-Dependent

As stated in the Introduction, the diversity of endophytic fungi includes two groups of fungi, the first of which is formed of members of the family *Clavicipitaceae*, a specific class of fungi that colonizes grasses as obligate biotrophic symbionts and can enhance the resistance of grasses to multiple stresses. *Epichloë* and *Neotyphodium* are remarkable genera of these clavicipitaceous endophytic fungi. The second group, named nonclavicipitaceous, clusters phylogenetically diverse fungi from Ascomycota, Mucormycota, and Basidiomycota. Whereas the second group has a broad spectrum of hosts and is transmitted predominantly in a horizontal way, members of the first group have a reduced spectrum of hosts and are transmitted vertically [3,22]. In this review, we focus on the more frequent nonclavicipitaceous endophytic fungi.

Endophytic fungi are highly diverse phylogenetically and have been found in all land plants studied today. *Penicillium*, *Alternaria*, *Fusarium*, *Colletotrichum*, *Aspergillus*, and *Xylaria* are the most frequently isolated genera [4]; however, other reports have detected *Alternaria*, *Colletotrichum*, *Fusarium*, *Gibberella*, *Glomerella*, *Guignardia*, *Leptosphaerulina*,

Nigrospora, *Phoma*, *Phomopsis*, and *Xylaria* [23]. It should be noted that the frequency of isolation of some genera depends on plant features, such as genotype, sampled tissue, geography, age, or season of sampling [24].

The diversity, specificity, and specialization of endophytic fungal communities are influenced both by geographic factors and by the genotype and ecological role of the host plant [5]. In a study with three native Hawaiian plants that co-occur along the elevation gradient (*Leptocophylla tameiameia*, *Marchantia polymorpha*, and *Vaccinium reticulatum*), different patterns of endophytic fungi diversity, host specificity and specialization of interaction were observed at different elevations: less specialization and more diversity at the extremes of elevation. That is, at the extremes the associations were less specific, observing the greatest specialization at the mid-elevation [25]. Similarly, in the medicinal plant *Glycyrrhiza glabra* from different locations in the North-Western Himalayas, geographic location plays an important role in the recruitment of endophytic fungal communities, with the highest species richness being observed in the subtropical region [26]. Additionally, in this same genus of plant, the availability of potassium, nitrogen, and the accumulation of water and liquiritin in the roots influence the configuration of the structure of the endophytic fungal communities. In pines, each species has its own structure of endophytic fungi; in other words, the richness and structure of endophytic fungi vary depending on the pine space and the height of the trunk. The most commonly isolated genera were *Trichoderma*, *Penicillium*, *Aspergillus*, *Mucor*, *Alternaria*, *Sphaeropsis*, *Fusarium*, and *Chaetomium*. *Trichoderma* was common to all endophyte communities [27].

Although we can find certain species inhabiting several tissues of a host plant simultaneously, it is believed that these strains are genetically distinct, so the true diversity and specificity of endophytic fungal communities among different tissues can be observed at the genotype level.

Unlike roots, bark or phloem leaves are biochemically more dynamic as they are exposed to environmental damage and play a critical role in photosynthesis; as a consequence, foliar endophytes have important differences from root, bark, or phloem endophytes, since the colonization of leaves occurs in a substantially different context in comparison to roots, for example [5]. The analysis of 1400 foliar endophytic fungi from boreal to tropical forests revealed high species richness, observing few species and many classes of endophytes in boreal forests, as well as few classes but many species in tropical forests [28]. Evidence shows that the diversity and richness of species of foliar endophytes from trees are influenced by a variety of factors, for example, the age of host tree, with older trees having more diversity and richness of species. [29,30]. A recent study of the hyperdiversity of foliar endophytes from tropical forests showed that fungal richness decreased linearly with temperature seasonality, and as a quadratic function for precipitation seasonality, supporting the vital role of climate in shaping hyperdiversity of foliar endophytic fungi [31].

4. Endophytic Fungal Association: An Interkingdom Crosstalk

Associations between plant and endophytic fungi involve a complex chemical interkingdom interaction including averting/suppressing the defense mechanisms of the host plant, the regulation of fungal virulence factors, and the mediation of coexistence with other fungi and bacteria inside the plant [32]. Thus, the host fungus downregulates some mechanisms and produces antagonistic secondary metabolites or chemical mediators to deal with competitors from the rest of the microbiome. This leads to multiple equilibria of balanced antagonisms and, therefore, contributes to the health of the host plant [33]. The plant–pathogen and plant–endophytic fungi interaction is the same during the first stages of contact; that is, both the pathogenic fungus and the endophyte produce virulence factors that will facilitate the colonization of the plant, while the plant responds with the defense mechanisms available. Unlike pathogenic fungi, which will continue to produce virulence factors until they colonize the plant and cause disease, endophytic fungi will modulate the production of virulence factors and will colonize the plant without disease symptoms (Figure 1). Additionally, the establishment of this association implies a process

of recruitment of microbes by the host plant and inter- and intraspecies interactions to modulate the plant's defense mechanisms [9]. The disequilibrium of the host plant–endophyte fungi relationship could compromise the health of the plant and become a pathogenic interaction [34,35]. The fate of the interaction is multifactorial, that is, whether the growth of the fungus is asymptomatic or will lead to disease depends on the adaptations of the fungus to a specific host or organ, on the endophyte and host states, on the innate but also variable endophyte virulence, the host defense response, and the environmental conditions [10,33,36]. Some observations have been made on the genomic level related to differences in the endophytic lifestyle evolution, for instance, comparative genomics of two Dark Septate Endophytes (DSE) (independently evolved in the same habitat) and 32 ascomycetes of different lifestyles showed that: first, DSE have larger genome sizes, in comparison with other ascomycetes, caused by expansion of the protein-coding gene inventory and expanded number of CAZymes, including plants cell wall degrading enzymes [37], in contrast to ectomycorrhizal fungi where the decay mechanisms are lost [38]; second, despite some similarities between the two DSE, low levels of convergence were observed in their gene family evolution, leading to marked functional heterogeneity within the endophytic lifestyle [37].

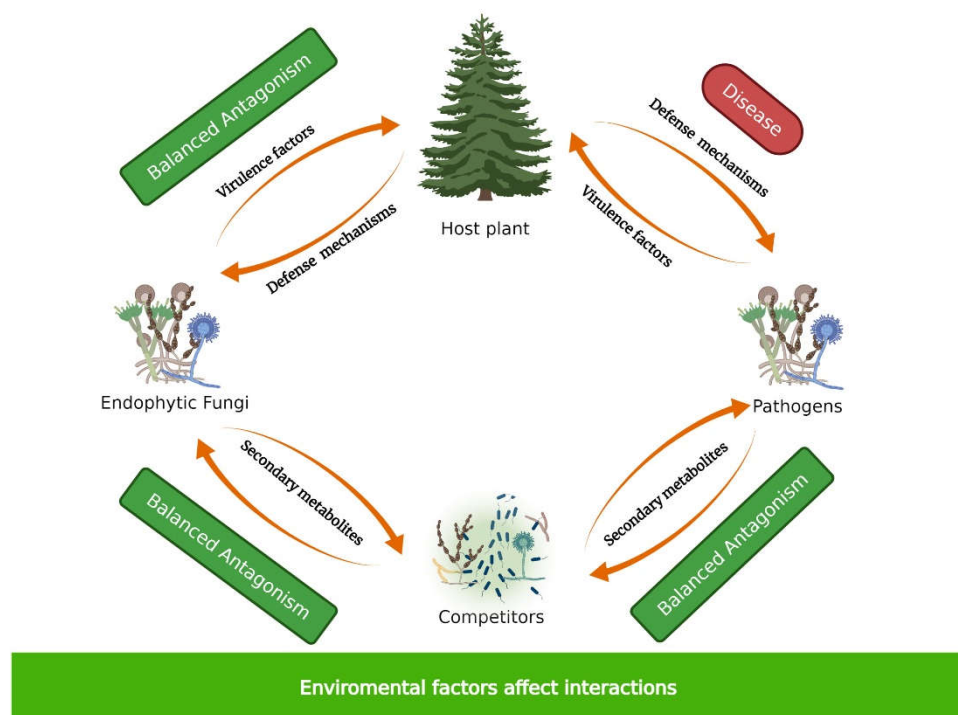


Figure 1. Multiple balanced antagonisms in endophytic fungi interactions. Created with [BioRender.com](https://www.biorender.com/), accessed on 3 September 2021.

5. Endophytism and Pathogenicity

Many strains of endophytic fungi belong to genera and species of typically pathogenic or saprophytic plant fungi. In a variety of plants, their endophytes are capable of causing disease in the host plant when environmental conditions change. Such is the case of endophytic *Arabidopsis thaliana* fungi, which behave as pathogens when tested under in vitro conditions [6]. Similarly, in *Marchantia polymorpha*, although most of its endophytes promote growth, some are aggressively pathogenic. Even isolates of the same genus have very varied effects on the plant (positive, negative, or neutral) [39]. Single-species fungal populations may contain strains with pathogenic, mutualistic, or neutral behavior in their host [7]. For example, a study of 181 strains of the plant pathogenic fungus *Fusarium verticillioides*, isolated from corn plants at different locations and growth stages, showed that

the growth cycle of the plant modulates the phytopathogenic behavior of the fungus, even behaving as a mutualistic endophyte. Regarding the characteristics of the isolated fungal populations, it was found that the phenological stages of corn act as a selection pressure for the fungi in favor of the plant [40]. This variability could be influenced by the genotypes of the host and the endophyte [41], the environmental conditions, the interactions among several endophytic fungi within the host plant [42], or by the presence of endobacteria or mycoviruses that can modulate the behavior of the fungus [43,44].

6. Endobacteria and Mycoviruses Can Modulate Endophytism

Endobacteria inhabiting endophytic and phytopathogenic fungi are associated with a positive effect on the performance of host fungi; in other words, endohyphal bacteria help to establish a pathogenic or symbiotic relationship with the host plant. [43]. For example, the symbiosis between the bacterium *Burkholderia rhizoxinica* and the phytopathogenic fungus *Rhizopus microsporus* leads to the production of rhizoxin, a potent antimitotic toxin that causes rice seedling blight [45], or rhizonin, a hepatotoxic cyclopeptide; both compounds help the fungus to set up infection [46]. A study revealed that *B. rhizoxinica* possesses a type III secretion system that is essential to maintain the bacterium–fungus symbiosis; moreover, the fungus strictly needs the bacterium for sporulation [47]. Further, recent research demonstrated that in addition to *B. rhizoxinica*–*R. microsporus* symbiosis, two narnaviruses are required for sexual reproductive success; in fact, narnaviruses decrease asexual reproduction of fungi [48]. In the case of endophytic fungi, a variety of endohyphal bacteria have been found in endophytic foliar fungi, mostly belonging to Proteobacteria [49]. The association of *Luteibacter* sp. with the endophytic fungus *Pestalotiopsis* aff. *neglecta* enhances the production of indole-3-acetic acid (IAA). During the culture of the pure bacterium, the presence of IAA was not observed [50].

The presence of mycoviruses is common in endophytic fungi and plant pathogenic fungi. These viruses are capable of regulating the virulence of phytopathogenic fungi (Table 1) [51]. This characteristic has been proposed as a promising strategy for the biological control of diseases in some crops. However, the use of these mycoviruses has been limited due to the little understanding that we still have about aspects such as transmission mechanisms, ecological impact, the effectiveness of their use in the field, and their persistence in the populations of fungi [44]. Recent studies have shown that mycoviruses, in addition to transforming pathogenic strains into hypovirulent ones, convert them into mutualistic endophytic fungi. As evidence, recently was demonstrated that the mycovirus SsHADV-1 from *Sclerotinia sclerotiorum*, a typically necrotrophic pathogen, converts the fungus into a beneficial endophyte [52]. Field experiments showed that the infected fungus promoted the growth of the host plant, improved its resistance to diseases and its yield. Similar behavior was observed with the pathogenic fungus *Pestalotiopsis theae* from *Camellia sinensis*: when it is infected with the mycovirus PtCV1, its pathogenicity is eliminated and the resistance of the host plant to the pathogenic strain of the fungus increases [53].

Table 1. Effect of viruses in fungi.

| Host Plants | Endophytic/Pathogenic Fungi | Mycoviruses | Effect in Host Plants | References |
|--------------------------|---------------------------------|---|--|------------|
| <i>Camellia sinensis</i> | <i>Pestalotiopsis theae</i> | chrysovirus-1 | Eliminates fungal virulence and confers disease resistance in plants | [53] |
| <i>Castanea dentata</i> | <i>Cryphonectria parasitica</i> | Cryphonectria hypovirus 1 (CHV1), Cryphonectria parasitica mitovirus 1 (CpMV1) | Hypovirulence | [54,55] |

Table 1. Cont.

| Host Plants | Endophytic/Pathogenic Fungi | Mycoviruses | Effect in Host Plants | References |
|--|---------------------------------|--|--|------------|
| More than 64 genera of plants | <i>Sclerotinia sclerotiorum</i> | Sclerotinia sclerotiorum hypovirulence-associated DNA virus 1 (SsHADV-1), Hubei sclerotinia RNA virus 1 (HuSRV1) | Hypovirulence, growth promotion, disease resistance, and improved yield of host plants | [52,56,57] |
| <i>Cucumis sativus</i> , <i>Fragaria</i> × <i>ananassa</i> , <i>Vitis</i> <i>vinifera</i> , <i>Lycopersicon</i> <i>esculentum</i> | <i>Botrytis cinerea</i> | Botrytis cinerea partitivirus 2 (BcPV2), Botrytis cinerea fusarivirus 1 (BcFV1) | Hypovirulence | [58,59] |
| <i>Zea mays</i> | <i>Fusarium graminearum</i> | Double-stranded RNA (dsRNA) | Hypovirulence | [60] |
| <i>Dichanthelium lanuginosum</i> | <i>Curvularia protuberia</i> | Curvularia thermal tolerance virus (CThTV) | Confers heat tolerance to host plant | [61,62] |
| <i>Brassica napus</i> | <i>Leptosphaeria biglobosa</i> | Double-stranded RNA quadrivirus | Hypovirulence, enhances systemic resistance to <i>Leptosphaeria maculans</i> | [63] |

7. Secondary Metabolism and Endophytism

Unlike primary metabolites (proteins, carbohydrates, fats, and nucleic acids) that are essentially the same in all organisms, secondary metabolites are found in specific groups of organisms or species. Further, sometimes these molecules are produced under specific conditions; on the other hand, their specific function in an organism or ecological niche is often unknown [64]. However, some metabolites have well-known functions as competitive chemicals that act against other organisms, as metal transporting agents, growth stimulants, hormones or differentiation effectors [65]. Particularly, endophytic fungi are a reservoir of a variety of secondary metabolites with unknown natural functions but interesting bioactivities [66]. Concerning trophic interactions, secondary metabolites may have roles in establishing beneficial endophytic interaction with the host plant. For instance, genomic comparison of the beneficial root endophyte, *Colletotrichum tofieldiae*, and its pathogenic relative, *Colletotrichum incanum*, revealed significant enrichment genes encoding secondary metabolites, and biosynthesis-related proteins in *C. tofieldiae* [67]. Likewise, transcriptomic and quantitative real-time PCR of the endophyte *Phomopsis liquidambari* B3, during colonization and growth promotion of rice and *A. thaliana*, showed that secondary metabolite genes are up-regulated in the endophytic state [68]. More detailed investigation indicated that genes farnesyl-diphosphate farnesyl transferase and squalene monooxygenase were significantly upregulated. It should be noted that these genes are involved in sesquiterpenoid and triterpenoid biosynthesis [69], suggesting a key role in the secondary metabolism of endophytic fungi during early interactions with host plants.

8. Terpenoids in Fungal Interactions

Terpenoids represent structurally diverse molecules and as the largest group of natural products derived from C₅ isoprene units, more than 80,000 terpenoids have been characterized from plant and microbial sources [70]. Biochemically, isoprene units may be derived through the mevalonic acid pathway (MVA) and methylerythritol phosphate pathway (MEP). According to their (C₅)_n skeleton, they are classified as hemiterpenoids (C₅), monoterpenoids (C₁₀), sesquiterpenoids (C₁₅), diterpenoids (C₂₀), sesterterpenoids (C₂₅), triterpenoids (C₃₀), and tetraterpenoids (C₄₀) [13,71]. Meroterpenoids are metabolites partially derived from terpenoids, for example, furocoumarins, retinoids, and ergot alkaloids [72].

The natural roles of terpenoids include antagonistic and beneficial interactions among organisms [71]. Particularly, fungal volatile terpenoids may play a key role in mediating endophytic fungi–host plant and endophytic fungi–microbiome interactions [14,73]. In general, volatile terpenoids are remarkable molecules interacting among different organisms. For example, fungal volatile sesquiterpenoids participate in the interaction with bacteria, other fungi, plants, and insects [14]. Patterns of fungal sesquiterpenoids and other volatile organic compounds (VOCs) emissions have been used to predict ecological function in several fungi (ectomycorrhizal, pathogens, and saprophytes) [74], supporting the role of terpenoids in fungal lifestyle [73].

Volatile sesquiterpenoid β -caryophyllene is emitted by *A. thaliana* flowers and acts as a defense against pathogens [75]. Similarly, *Allium sativum* produces volatile terpenes with antifungal properties in response to infection with *Sclerotium cepivorum*. Additionally, *Talaromyces wortmannii* promotes growth and pathogen resistance of *Brassica campestris* L. var. *perviridis* by β -caryophyllene production (Figure 2A) [76]. In contrast to these results, neutral effects of β -caryophyllene in a mix of VOCs emitted by *Fusarium oxysporum* strains were observed in *A. thaliana* plants [77]. However, β -caryophyllene can induce global changes in the plant microbiome. For instance, *Bacillus amilolicuefaciens* induces the production of β -caryophyllene: as a consequence, host plants produce a large amount of salicylic acid. Interestingly, β -caryophyllene together with other VOCs modified the composition of rhizospheric microbes of surrounding plants [78]. Similarly, another work demonstrated that infected *Carex arenaria* plants produced VOCs in roots that stimulated the attraction of surrounding soil bacteria [79].

Other volatile terpenoids also modify the global metabolism of surrounding organisms. Metabolomic analysis of volatiles from *Fusarium culmorum* showed that several volatile terpenoids can induce or reduce the motility of *Collimonas pratensis* Ter291 and *Serratia plymuthica* PRI-2C [80]. Transcriptomic analysis revealed changes in gene and protein expression related to motility, signal transduction, energy metabolism, cell envelope biogenesis, and secondary metabolite production (Figure 2B). More detailed experiments exhibited bacterial production of sodorifen, an unusual volatile terpenoid [81]. Sodorifen is assumed to constitute the long-distance communication molecules among some bacteria [82]. These findings reveal that bacteria sense and respond to fungal volatile terpenoids and suggest the importance of volatiles as signaling molecules in fungal–bacterial interactions over long distances [80,81]. A similar role of monoterpenoids and sesquiterpenoids has been observed in plant–rhizosphere [83], bacteria–bacteria [84], and bacteria–protists interactions [85].

Some fungal terpenoids act as plant growth-promoting agents and as signaling molecules in the early stage of mutualistic interaction among plants and fungi. Typical ectomycorrhizal fungi, such as *Laccaria bicolor*, produce biologically active sesquiterpenoids while interacting with *Populus* sp. or *Arabidopsis* sp. plants, stimulating lateral root production (Figure 2C), an important pre-colonizing step occurring even before any physical contact between the fungus and the plant. More exhaustive experiments showed that sesquiterpenoid (–)-thujopsene can stimulate lateral root formation in absence of fungi, confirming the role of sesquiterpenoids in early mutualistic interactions [86]. Additionally, many volatile terpenoids function in specific mixes for promoting plants' growth. For instance, *Trichoderma viride* produced 51 VOCs (among them seven sesquiterpenoids and one monoterpene) that positively influenced plant height, flowering, number of lateral roots, and biomass of *A. thaliana* (Figure 2D). Production of these compounds was independent of physical contact among plants and fungi [87]. A more detailed investigation revealed that VOCs of nine strains of *Trichoderma* sp. emitted more than 141 unique compounds, including several unknown sesquiterpenoids, diterpenoids, and tetraterpenoids. Blends of VOCs were strain-specific. Interestingly, biostimulatory strains tend to produce a larger number of complex terpenoids such as β -acoradiene, β -cubebene, β -cedrene, β -bisabolene, β -himachalene, and γ -himachalene [88].

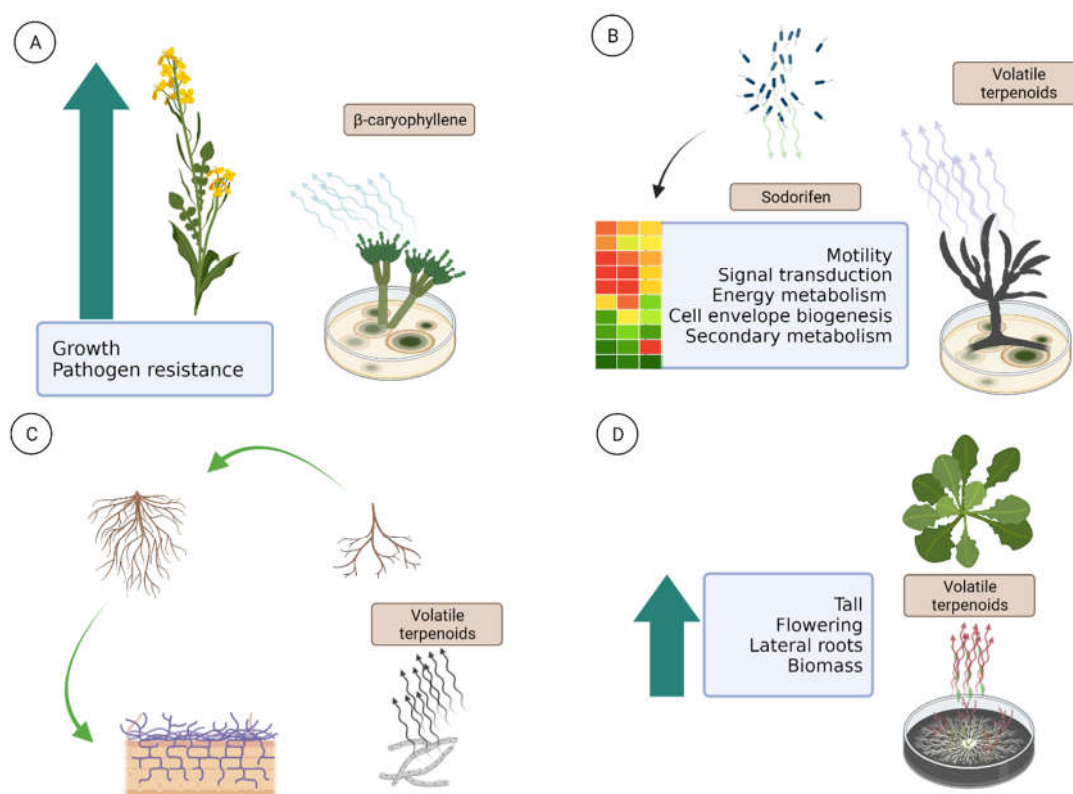


Figure 2. Natural role of fungal terpenoids. (A) Effects of fungal β -caryophyllene on *Brassica campestris*; (B) bacteria sensing and responding to fungal volatile terpenoids; (C) volatile terpenoids stimulating lateral root production; (D) effect of fungal terpenoids blend in *Arabidopsis*. Created with BioRender.com.

Studies on endophytic fungal volatile terpenoids are still limited. Understanding the natural role and evolutionary aspects of these compounds will lead to applications of terpenoids to agriculture and ecosystem management [73,89].

9. Endophytic Fungal Terpenoids as Bioactive Molecules

The bioactivities of terpenoids include anticancer, anti-inflammatory, antibacterial, antiviral, and antimalarial effects, as well as hypoglycemic activities. Recent studies suggest their potential application as insect resistance, immunoregulation, antioxidation, antiaging, and neuroprotection agents [90]. Approximately one-third of all terpenoids included in the Dictionary of Natural Products (a compendium which provides properties and complete history of the relevant literature for over 328,000 natural compounds) have antineoplastic-related activities [91]. Despite the fact that many terpenoids show a variety of important activities, the molecular mechanisms of most terpenoids remain unclear; therefore, more studies on the mechanistic of activities are essential for a better understanding and application of these structurally diverse molecules [92]. In Tables 2–5 below, we summarize the bioactive terpenoids isolated from endophytic fungi of medicinal plants, mangroves, algae, and some trees, mosses, and crops reported from 2017 to the first third of 2021 (Tables 2–5).

Table 2. Bioactive terpenoids isolated from endophytic fungi of medicinal plants.

| Host Plant | Endophyte | Bioactivity | Class of Terpenoid | References |
|--|---|---|--------------------|------------|
| <i>Phyllanthus glaucus</i> | <i>Phomopsis</i> sp. TJ507A | Inhibition of BACE1 | | [93] |
| <i>Hypericum ascyron</i> | <i>Phomopsis prunorum</i> | Antibacterial | | [94] |
| <i>Ligusticum wallichii</i> | <i>Aspergillus fumigatus</i> | Cytotoxic | | [95] |
| <i>Artemisia argyi</i> | <i>Trichoderma virens</i> QA-8 | Antimicrobial | | [96] |
| <i>Tylophora ovata</i> | <i>Aspergillus flavus</i> | Cytotoxic and hepatic protection effects | | [97] |
| <i>Panax notoginseng</i> | <i>Leptosphaeria</i> sp. XL026 | Antibacterial | Sesquiterpenoid | [98] |
| <i>Aconitum vilmorinianum</i> | <i>Phoma</i> sp. | Antiviral (H1N1) | | [99] |
| <i>Morinda officinalis</i> | <i>Trichoderma koningiopsis</i> A729 | Antibacterial and cytotoxic | | [100] |
| <i>Edgeworthia chrysantha</i> | <i>Penicillium purpurogenum</i> | Inhibition of pancreatic lipase | | [101] |
| <i>Panax notoginseng</i> | <i>Emericella</i> sp. XL 029 | Antimicrobial | | [102] |
| <i>Panax notoginseng</i> | <i>Preussia isomera</i> | Antibacterial | | [103] |
| <i>Panax notoginseng</i> | <i>Leptosphaeria</i> sp. XL026 | Antibacterial | | [98] |
| <i>Huperzia serrata</i> | <i>Penicillium chrysogenum</i> MT-12 | Inhibition of activity on ATP release of thrombin-activated platelets | | [104] |
| <i>Illigera rhodantha</i> | <i>Phomopsis</i> sp. S12 | Anti-inflammatory | | [105] |
| <i>Colquhounia coccinea</i> var. <i>mollis</i> | <i>Trichoderma atroviride</i> | Antibacterial activity and cytotoxic | | [106] |
| <i>Zingiber officinale</i> | <i>Penicillium</i> sp. ZO-R1-1 | Cytotoxic | Diterpenoid | [107] |
| <i>Panax notoginseng</i> | <i>Drechmeria</i> sp | Antimicrobial | | [108] |
| <i>Gliricidia septium</i> | <i>Nectria pseudotrichia</i> 120-1NP | Cytotoxic | | [109] |
| <i>Morinda officinalis</i> | <i>Trichoderma koningiopsis</i> A729 | Antibacterial and cytotoxic | | [100] |
| <i>Clerodendrum canescens</i> | <i>Pestalotiopsis adusta</i> | Cytotoxic | | [110] |
| <i>Salvia miltiorrhiza</i> | <i>Talaromyces pinophilus</i> | Antimicrobial activity | | [111] |
| <i>Lycium barbarum</i> | Strain L1-2 | Cytotoxic | | [112] |
| <i>Hypericum perforatum</i> | <i>Aspergillus</i> sp. TJ23 | Potentiator of oxacillin | | [113] |
| <i>Hypericum perforatum</i> | <i>Aspergillus</i> sp. TJ23 | Antibacterial Potentiator of oxacillin | | [114] |
| <i>I. eriocalyx</i> var. <i>laxiflora</i> | <i>Penicillium</i> sp. sh18 | Cytotoxic. Inhibition of tubulin polymerization | Meroterpenoid | [115,116] |
| <i>Acorus tatarinowii</i> | <i>Phyllosticta</i> sp. | Antimicrobial | | [117] |
| <i>Tripterygium wilfordii</i> | <i>Aspergillus</i> sp. | Immunosuppressive | | [118] |
| <i>Handroanthus impetiginosus</i> | <i>Talaromyces purpurogenus</i> H4 and <i>Phanerochaete</i> sp. H2 | Trypanocidal | | [119] |
| <i>Tripterygium wilfordii</i> | <i>Aspergillus terreus</i> Thom | Inhibition of BACE-1 and AchE | | [120] |
| <i>Hypericum perforatum</i> | <i>Emericella</i> sp. TJ29 | Cytotoxic | | [121] |
| <i>Withania somnifera</i> | <i>Colletotrichum gigasporum</i> | Inhibition of pancreatic lipase | | [122] |
| <i>Centella asiatica</i> (L.) Urban | <i>Colletotrichum gloeosporioides</i> | Cytotoxic and immunomodulatory | Triterpenoid | [123] |
| <i>Kadsura angustifolia</i> | <i>Trichoderma harzianum</i> SWUKD3.1610 | Inhibition of HIV-1 Reverse Transcriptase and Cytotoxic | | [124] |
| <i>Zingiber cgriffithii</i> Baker | <i>Hypomontagnella monticulosa</i> Zg15SU | Cytotoxic | | [125] |
| <i>Panax notoginseng</i> | <i>Preussia isomera</i> | Antibacterial | Sesterterpenoid | [103] |
| <i>Paeonia lactiflora</i> Pallas | <i>Alternaria tenuissima</i> , <i>Aspergillus flavus</i> , and <i>Penicillium commune</i>) | Anti-inflammatory | | [126,127] |
| <i>Ferula ovina</i> | <i>Pithoascus persicus</i> , <i>Ochroconis ferulica</i> , <i>Alternaria petroselini</i> , <i>Lasiobolium</i> sp. Nov., <i>Clonostachys rosea</i> , <i>Laburnicola</i> sp. Nov., <i>Phaeoacremonium</i> sp. <i>Cadophora interclivum</i> | Cytotoxic | Monoterpenoid | [128,129] |

Table 3. Bioactive terpenoids isolated from endophytic fungi of mangrove.

| Host Plant | Endophyte | Bioactivity | Class of Terpenoid | References |
|-------------------------------|------------------------------------|---|--------------------|------------|
| <i>Acrostichum aureum</i> | <i>Rhinochloidiella similis</i> | Cytotoxic | Sesquiterpenoid | [130] |
| <i>Kandelia obovata</i> | <i>Aspergillus flavus</i> QQSG-3 | Inhibition of α -glucosidase | | [131] |
| <i>Ceriops tagal</i> | <i>Penicillium</i> sp. J-54 | Cytotoxic | | [132] |
| <i>Kandelia candel</i> | <i>Diaporthe</i> sp. QYM12 | Anti-inflammatory | | [133] |
| <i>Xylocarpus moluccensis</i> | <i>Aspergillus</i> sp. xy02 | Antibacterial | | [134] |
| <i>Ceriops tagal</i> | <i>Cytospora</i> sp. | Antimicrobial | Diterpenoid | [135] |
| <i>Kandelia candel</i> | <i>Diaporthe</i> sp. QYM12 | Anti-inflammatory | | [133] |
| <i>Kandelia obovata</i> | <i>Talaromyces amestolkiae</i> YX1 | Anti-inflammatory activity | | [136] |
| <i>Sonneratia apetala</i> | <i>Aspergillus</i> sp. 16-5c | Inhibition of AchE | Meroterpenoid | [137] |
| <i>Kandelia obovata</i> | <i>Aspergillus terreus</i> H010 | Anti-inflammatory | | [138] |
| <i>Bruguiera sexangula</i> | <i>Phyllosticta capitalensis</i> | Antimicrobial | | [139] |
| <i>Kandelia candel</i> | <i>Aspergillus</i> sp. ZJ-68 | Anti-inflammatory and inhibition of PtpB from <i>Mycobacterium tuberculosis</i> | Sesterterpenoid | [140] |

Table 4. Bioactive terpenoids isolated from endophytic fungi of alga.

| Host Plant | Endophyte | Bioactivity | Class of Terpenoid | References |
|-------------------------------|---------------------------------------|-------------------------------------|--------------------|------------|
| <i>Laminaria japonica</i> | <i>Trichoderma harzianum</i> X-5 | Antiphytoplankton | Sesquiterpenoid | [141] |
| <i>Pterocladia capillacea</i> | <i>Chondrostereum</i> sp. NTOU4196 | Anti-inflammatory in microglial | | [142] |
| <i>Sargassum</i> sp. | <i>Trichoderma asperellum</i> cf44-2 | Antibacterial and Antiphytoplankton | | [143] |
| <i>Laminaria japonica</i> | <i>Trichoderma harzianum</i> X-5 | Antiphytoplankton | Diterpenoid | [141] |
| <i>marine-derived</i> | <i>Aspergillus porosus</i> | Antibacterial | | [144] |
| <i>Leathesia nana</i> | <i>Penicillium chrysogenum</i> XNM-12 | Antimicrobial | Meroterpenoid | [145] |
| <i>Rhodomela confervoides</i> | <i>Aspergillus</i> sp. RR-YLW-1 | Antimicroalgae | | [146] |
| <i>Rhodomela confervoides</i> | <i>Aspergillus</i> sp. RR-YLW-1 | Antimicroalgae | Sesterterpenoid | [146] |
| <i>Sargassum</i> sp. | <i>Trichoderma asperellum</i> cf44-2 | Antibacterial and Antiphytoplankton | Monoterpenoid | [143] |

Table 5. Bioactive terpenoids isolated from endophytic fungi of diverse plants.

| Host Plant | Endophyte | Bioactivity | Class of Terpenoid | References |
|---|------------------------------------|---|-------------------------------|------------|
| <i>Elaeocarpus decipiens</i> Hemsl (tree) | <i>Aspergillus versicolor</i> | Antimicrobial | Sesquiterpenoid | [147] |
| <i>Oxytropis glabra</i> (desert plant) | <i>Alternaria oxytropis</i> | Retarded seedling growth of <i>Arabidopsis thaliana</i> | Sesquiterpenoid | [148] |
| <i>Rhodobryum umgiganteum</i> (moss) | <i>Botryosphaeria laricina</i> | Induction of quinone reductase | Diterpenoid and meroterpenoid | [149–151] |
| <i>Toona sinensis</i> (tree) | <i>Xylaria</i> sp. XC-16 | Allelopathic | Diterpenoid | [152] |
| <i>Cephalotaxus fortune</i> (tree) | <i>Phyllosticta capitalensis</i> | Phytotoxic | Meroterpenoid | [153] |
| <i>Dendrobium nobile</i> (ornamental) | <i>Guignardia mangiferae</i> TJ414 | Anti-inflammatory | Meroterpenoid | [154] |
| <i>Kageneckia angustifolia</i> (Ornamental) | <i>Penicillium</i> sp. SWUKD4.1850 | Cytotoxic | Triterpenoid | [155] |
| <i>Polytrichum commune</i> (moss) | <i>Diplodia cupressi</i> | Cytotoxic | Triterpenoid | [156] |
| <i>Laptozpermum brachyandrum</i> (tree) | <i>Eutypella scoparia</i> SCBG-8 | Antibacterial (MRSA) | Triterpenoid | [157] |
| <i>Triticum</i> (crop) | <i>Bipolaris</i> sp. TJ403-B1 | Antimicrobial and anti-inflammatory | Sesterterpenoid | [158,159] |
| <i>Cucumis sativus</i> (crop) | <i>Paecilomyces formosus</i> LHL10 | Inhibition of α -glucosidase and urease | Sesterterpenoid | [160] |

Although a three-year period may be too short to obtain a representative analysis, Basidiomycota are the most abundant endophytic fungi producing bioactive terpenoids in this review (97.4%). They were grouped in 13 orders: *Eurotiales* (40%), *Hypocreales* (16%), *Diaporthales* (12%), *Pleosporales* (12%), *Botryosphaeriales* (10.7%), *Xylariales* (4%), *Glomerellales* (2.7%), *Chaetothyriales* (1.3%), *Helotiales* (1.3%), *Microascales* (1.3%), *Pezizales* (1.3%), *Togniniales* (1.3%), and *Venturiales* (1.3%). The most frequently isolated fungi belong to *Eurotiales*, being *Aspergillus* and *Penicillium* the predominant species. In addition, 50% of all species in this review are included in two families, *Trichocomaceae* and *Hypocreaceae*.

10. Endophytic Fungi Biosynthesize Important Therapeutic Drugs

In general, microbes produce a collection of secondary metabolites with therapeutic activities. Many are used as anticancer, immunosuppressive, hypocholesterolemic, antiparasitic, anti-inflammatory agents, or as enzyme inhibitors [161,162]. Indeed, endophytic fungi have become a treasure trove for bioactive compounds of medicinal and agricultural importance [163]. Several endophytic fungi produce important therapeutic drugs, initially discovered in traditional medicinal plants (Table 6); for example, paclitaxel, podophyllotoxin, *Vinca alkaloids*, camptothecin, and fusidic acid [163].

10.1. Paclitaxel

Paclitaxel is possibly the most famous natural product of endophytic fungi. This highly functionalized diterpenoid is a potent antimitotic compound originally isolated from the stem bark of the western yew, *Taxus brevifolia*. It was the first natural substance that demonstrated antimycotic, antileukemic, and tumor inhibitory activities [164]. In 1993, the first endophytic fungi producing paclitaxel was reported. *Taxomyces andreanae* was isolated from the inner bark of *T. brevifolia* and produced paclitaxel and related compounds when grown in a semisolid synthetic medium [165]. Frequently, paclitaxel-producing endophytic fungi have been isolated from different sources other than *Taxus* trees, even at a higher concentrations than those isolated from *Taxus* trees; such is the case of studies focused on endophytes from plants used in traditional medicine [166–169]. For example, *Cladosporium oxysporum*, isolated from the medicinal plant *Moringa oleifera* yields 550 µg/L in liquid fermentation [170], a high concentration considering that *Taxomyces andreanae* yielded 0.05 µg/L at similar culture conditions. Likewise, *Phoma betae* from Ginkgo biloba leaves yielded 795 µg/L [168]. Now, hundreds of fungi isolated from yew and other plants have been shown to produce paclitaxel [171], including patents for the production of paclitaxel from endophytic fungi focused on optimization of the production process, methods for purification from the fermentation broth, and methods for screening paclitaxel-producing endophytic fungi [172].

10.2. Podophyllotoxin

Podophyllotoxin is an aryltetralin–lignan anticancer metabolite produced by several plants, mainly by *Sinopodophyllum hexandrum*; it is used in the East and Middle East as traditional medicine. Podophyllotoxin serves as a precursor to three key chemotherapeutic drugs: etoposide, teniposide, and etoposide phosphate [173]. Etoposide is widely used to treat various types of cancer and has recently been proposed as an adjunct treatment to immunosuppressants for critically ill COVID-19 patients [174,175]. Several endophytic fungi from different plant species have been reported to produce podophyllotoxin at different concentrations; likewise, two patents concerning methods for the identification of podophyllotoxin-producing fungi and production and recuperation processes of podophyllotoxin in liquid fermentation have been issued [172].

10.3. Vinca alkaloids

Vinca alkaloids (vincristine and vinblastine) and semisynthetic derivatives (vinorelbine, vindesine, and vinflunine) are remarkable antimitotic chemotherapeutics utilized in the treatment of hematological and lymphatic neoplasms. These indole terpenoids stop mitosis

by inhibiting the formation of microtubules (at low concentration) or depolymerizing microtubules (at high concentrations) [176]. Some fungi produce vinblastine or vincristine under specific culture conditions, such as *Botryosphaeria laricina* CRS1, an endophyte of *Catharanthus roseus*, in which high yields of vinblastine and vincristine are dependent on elicitors present in extracts of the host plant [177]. In the case of *Alternaria alternata* and *Talaromyces radius*, the yield of vinblastine depends on media composition [178,179]. Despite the fact that *Catharanthus roseus* has many endophytic fungi, only some of them have been demonstrated to produce vinblastine or vincristine [180,181]. Other approaches include the use of endophytes to elicit the accumulation of *Vinca alkaloids* in the leaves of *C. roseus*. Inoculation of these plants with two of their endophytes (*Curvularia* sp. CATDLF5 and *Choanephora infundibulifera* CATDLF6) was found to enhance vindoline content by upregulating genes related to the terpenoid indole alkaloid biosynthesis in *C. roseus* [182]. Similar results were observed in cell suspension cultures of the same plant [183].

10.4. Camptothecin

Together with paclitaxel and *Vinca alkaloids*, camptothecin (including its analogs) belongs to the most important chemotherapeutic drugs. Camptothecin is an indole-terpene alkaloid extracted from the bark of *Camptotheca acuminata* [184], used as the precursor of two more potent camptothecin analogs: topotecan, and irinotecan. Different from the previously described substances, which are antimetabolic drugs, camptothecins belong to the group of topoisomerase inhibitors, particularly camptothecins that act by inhibiting DNA topoisomerase I, an enzyme found in significantly high levels in many cancer surgical specimens [176,185]. Commercially, camptothecin is extracted from *C. acuminata* and *Nothapodytes nimmoniana* with yields up to 0.3% of dry weight [186]. Most endophytic camptothecin-producing fungi have been isolated from those host plants (Table 6). *Aspergillus niger*, *Alternaria alternata*, and *Fusarium solani* were isolated from *Piper betle*, *Miquelia dentata*, and *Apodytes dimidiata*, respectively [187–189]. The highest yield was obtained from *Trichoderma atroviride* LY357, isolated from *C. acuminata*, about 197.82 µg/L [190]. Despite the high yield among endophytic fungi, it is little exploited in industry [191].

10.5. Fusidic Acid

Fusidic acid is an antibiotic isolated in 1962 from the fermentation broth of a strain of *Fusidium coccineum* [192]. Chemically, it is a fusidane triterpenoid inhibitor of prokaryotic elongation factor (EF-G), hence it stops protein synthesis [193]. This antibiotic is particularly important in infections by staphylococci, including the methicillin-resistant *Staphylococcus aureus* (MRSA) [194]. Recently, the endophytic fungus *Acremonium pilosum* F47 has been reported to produce authentic fusidic acid, two known analogs (16-desacetylfusidic acid and 3β,20-dihydroxy-protosta-16,24-dien-29-oic acid), and a new derivative, acremonidiol A. [195]. A few more fungi, such as *Sarocladium oryzae*, an endophyte of *Oryza rufipogon* Griff. (Dongxiang wild rice) [196], and *Xylaria* sp., endophyte of *Anoectochilus setaceus* [197], have been shown to produce other fusidane-type antibiotics, including helvolic acid.

Table 6. Endophytic fungi that produce important therapeutic drugs.

| Secondary Metabolite | Representative Endophytic Fungi | References |
|---|--|-------------------|
| Paclitaxel (anticancer chemotherapy drug) | <i>Aspergillus candidus</i> , <i>Chaetomella raphigera</i> , <i>Cladosporium cladosporioides</i> , <i>Cladosporium oxysporum</i> , <i>Lasioidiplodia theobromae</i> , <i>Penicillium aurantiogriseum</i> , <i>Periconia</i> sp., <i>Pestalotiopsis microspora</i> , <i>Pestalotiopsis versicolor</i> , <i>Phoma betae</i> , <i>Phomopsis</i> sp., <i>Phomopsis</i> sp., <i>Phomopsis</i> sp., <i>Phyllosticta citricarpa</i> , <i>Phyllosticta melochiae</i> | [168–170,198–207] |

Table 6. Cont.

| Secondary Metabolite | Representative Endophytic Fungi | References |
|--|---|-------------------|
| Camptothecin and analogs (anticancer chemotherapy drug) | <i>Fusarium solani</i> , <i>Fusarium oxysporum</i> , <i>Entrophospora infrequens</i> , <i>Trichoderma atroviride</i> , <i>Neurospora</i> sp., <i>Alternaria alstroemeriae</i> , <i>Alternaria burnsii</i> , <i>Alternaria</i> sp., <i>Alternaria alternata</i> , <i>Xylaria</i> sp., <i>Aspergillus</i> sp., <i>Aspergillus niger</i> | [187–190,208–215] |
| Vinblastine and vincristine (anticancer chemotherapy drug) | <i>Alternaria alternata</i> sp, <i>Fusarium oxysporum</i> , <i>Talaromyces radicus</i> , <i>Curvularia verruculosa</i> , <i>Botryosphaeria laricina</i> | [177–179,216,217] |
| Podophyllotoxin (anticancer chemotherapy) | <i>Phialocephala fortinii</i> (0.5 to 189 µg/L), <i>Alternaria tenuissima</i> , <i>Mucor fragilis</i> , <i>Trametes hirsuta</i> , <i>Alternaria</i> sp. <i>Fusarium solani</i> | [218–223] |
| Fusidic acid (antibiotic) | <i>Acremonium pilosum</i> | [195] |

11. Challenges and Future Perspectives

Although many endophytic fungal strains reach relatively high yields, and there are at least 28 patents available regarding the production of pharmaceutically important secondary metabolites [172], complex challenges remain related to the poor understanding of the biochemical, molecular, and evolutionary principles driving the biosynthesis of bioactive molecules [224].

Many limitations for the use of secondary metabolites from endophytic fungi stem from poor understanding of endophytism. As a consequence, we do not clearly understand the ecological role of most secondary metabolites, and questions emerge regarding how biosynthesis of certain metabolites is regulated. Does this regulation depend only on the endophyte or the host plant? Or both? How do environmental factors, such as biotic and abiotic stress, influence the production of a specific secondary metabolite? All these questions are key during the design of industrial production processes [225,226]. More generally, our knowledge and understanding of the biology of many fungi is limited. Therefore, there are limited numbers of molecular and synthetic biology tools, high-throughput technologies, and high-quality annotated and curated fungal genomes [227]. As noted above, challenges in the use of bioactive terpenoids and other secondary metabolites are complex, thus, more multidisciplinary research in fungal biology and biotechnology is needed.

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