

*Review*

## Plant Bioactive Metabolites and Drugs Produced by Endophytic Fungi of Spermatophyta

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**Abstract:** It is known that plant-based ethnomedicine represented the foundation of modern pharmacology and that many pharmaceuticals are derived from compounds occurring in plant extracts. This track still stimulates a worldwide investigational activity aimed at identifying novel bioactive products of plant origin. However, the discovery that endophytic fungi are able to produce many plant-derived drugs has disclosed new horizons for their availability and production on a large scale by the pharmaceutical industry. In fact, following the path traced by the blockbuster drug taxol, an increasing number of valuable compounds originally characterized as secondary metabolites of plant species belonging to the Spermatophyta have been reported as fermentation products of endophytic fungal strains. Aspects concerning sources and bioactive properties of these compounds are reviewed in this paper.

**Keywords:** plant-derived drugs; bioactive compounds; endophytic fungi

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## 1. Introduction

Endophytic fungi are polyphyletic microorganisms that inhabit plant tissues without inciting disease symptoms, and eventually establish mutualistic associations with their host plants. Until recently these microbial entities have been generally overlooked as a component of ecosystems, the reason why lately they have been regarded as a trove of unexplored biodiversity. Investigations on the biosynthetic potential of endophytes have gained impetus owing to the ongoing discovery of strains capable to synthesize plant compounds, a property which may reflect an adaptative functional role in biocenosis. The intrinsic nature of the interactions among and between endophytes and host plants, and pests, which are mediated by such compounds, is an area open to future discoveries. The elucidation of such connections can not only enhance the understanding of evolution of complex defense mechanisms in plants and their associated organisms, but also help to exploit the latter for a sustained production of a few valuable compounds to be used in biotechnologies [1].

Secondary metabolites serve in multiple physiologic functions, many of which are common to both plants and microorganisms, and in a way it is intuitive that the same or similar compounds can be produced by ecologically associated entities. Thus, the aim to exploit botanical diversity for the discovery of novel drugs has led to the finding of microbial strains able to synthesize bioactive compounds previously considered as typical plant products. In the last 25 years, the general evidence that all plants are inhabited by endophytic microorganisms, together with an ongoing finding that the latter are also capable of producing plant metabolites, has depicted a research context which is more inclined to consider these compounds as a major factor influencing the establishment and evolution of mutualistic interrelations. Moreover, a refined tool enabling endophytes to regulate the metabolism of host plants in their delicately balanced association [2].

This paper offers an overview on the extremely varied assortment of organic molecules occurring as secondary metabolites both in plants and endophytic fungi. Our attention is particularly focused on products occurring in single or a restricted range of plant species, with a few exceptions. Therefore, compounds representing metabolic products of a wide array of organisms, such as carbohydrates, aliphatic compounds, aminoacids, peptides, nucleobases, phenolic and benzoic acids, tannins and pseudotannins, sterols, and carotenoids, are not treated in this review.

## 2. Phytohormones

Plant hormones are undoubtedly among the main secondary metabolites that can influence plant fitness and enhance development when exogenously administered. Many fungal species have been reported to be able to produce compounds such as indole-3-acetic acid (IAA) and gibberellins (GAs), particularly species inhabiting rhizosphere which are presumed to exert a consistent effect on plant development [3]. Likewise, the observation of such an aptitude by endophytic fungal strains, which in most instances establishes an even closer association with plant tissues, is indicative of a possible functional meaning of mutualistic relationships in certain associations, and provides ground for a more direct impact of an exogenous provision of phytohormones. Unlike what is generally thought for other products synthesized by both plants and endophytes, experimental findings have shown that biosynthetic pathways for these compounds may have evolved independently in plants and fungi [4,5].

The interaction of crop plants with endophytic fungi producing gibberellins could be exploited as a strategy to overcome the adverse effects of abiotic stresses, considering the increased plant growth and biomass production that have been documented even in extreme environmental conditions [6]. On the other hand, it must be considered that hormones are characterized by a dose-related effect, the reason why exceeding supplies may result into abnormal growth. In fact, gibberellins were discovered as products of the plant pathogenic fungus *Fusarium* (= *Gibberella*) *fujikuroi* inducing disease symptoms (elongation of internodes, leaf yellowing, etc.) in rice plants [7]. Until recently, a number of fungal plant pathogens have proved to be able to produce these phytohormones as a means for altering physiology of their hosts, but these cases are not a subject for this review. We also do not consider the complex case of the endophytic fungi inhabiting a series of fodder plants, which cause noxious effects to livestock because of their attitude to permeate host tissues with mycotoxins, and are also able to produce phytohormones [8–10]. A few excellent reviews on this bordering subject are available in the literature [11–13].

Production of IAA by fungi establishing a mutualistic relationship with plants was first evidenced by a few mycorrhizal species recovered from pine and orchid roots [14–16]. Afterwards it has been reported by strains of *Colletotrichum* sp. from *Artemisia annua* [17], *Talaromyces verruculosus* (= *Penicillium verruculosum*) from roots of *Potentilla fulgens* [18], and *Penicillium glabrum* from pomegranate (*Punica granatum*) fruits [19]. An isolate of the yeast *Williopsis saturnus* endophytic in maize roots was found to produce IAA and indole-3-pyruvic acid [20]. Finally, IAA is also produced by *Piriformospora indica* [21], the quite famous Basidiomycetes species first described as a mycorrhizal agent of shrubs growing in the Rajasthan desert [22], but later found to be widespread and able to colonize roots of many host plants, disclosing a potential for applications in crop production [23]. However, all these reports should be carefully verified considering the growth medium used for culturing the producing strains; in fact, it has been observed that the addition of tryptophan incited auxin synthesis by a couple of yeast strains of *Rhodotorula graminis* and *R. mucilaginosa* recovered from poplar stems [24].

Other endophytic fungi have been found to produce both IAA and GAs, such as two strains of *Fusarium* sp. from *Euphorbia pekinensis* [25]. Moreover, a strain of *Galactomyces geotrichum* isolated from the aquatic plant *Trapa japonica* produced IAA and biologically active GAs (GA<sub>1</sub>, GA<sub>4</sub>, and GA<sub>7</sub>) [26], while two strains from cucumber roots (*Phoma glomerata* and *Penicillium* sp.) were found to produce gibberellic acid (GA<sub>3</sub>) along with GA<sub>1</sub>, GA<sub>4</sub>, GA<sub>7</sub>, and IAA in Czapek-Dox broth. This medium is based on sucrose as the only organic compound, which demonstrates an intrinsic ability by these strains to synthesize phytohormones. When experimentally inoculated in cucumber plants under drought stress, the plant biomass and related growth parameters significantly increased, together with a higher assimilation of essential nutrients (K, Ca and Mg), while effects of sodium toxicity were reduced. Moreover, a modulation of stress was also ensured through alteration in jasmonic acid level, down-regulation of abscissic acid, and increased salicylic acid content [27]. Similar effects resulted in the evaluation of another cucumber endophytic strain (*Paecilomyces formosus*) by the same research group [28].

Production of GAs only has been documented in a higher number of endophytic fungi. A strain of *Fusarium proliferatum* from roots of *Physalis alkekengi* var. *francheti* displayed a plant growth-promoting activity twice stronger than a wild-type of *F. fujikuroi*, due to the production of the physiologically

active GA<sub>1</sub>, GA<sub>3</sub>, GA<sub>4</sub>, and GA<sub>7</sub>, along with GA<sub>9</sub>, GA<sub>20</sub> and GA<sub>24</sub> [29]. Another strain of *F. proliferatum* from orchid roots was found to produce GA<sub>4</sub> and GA<sub>7</sub> as the major forms, and smaller amounts of GA<sub>1</sub>, GA<sub>3</sub>, GA<sub>9</sub>, GA<sub>13</sub>, GA<sub>14</sub>, GA<sub>16</sub>, GA<sub>24</sub>, GA<sub>25</sub>, and GA<sub>36</sub>, together with additional side products in the GA-biosynthetic pathway [30]. A strain of *Scolecobasidium tshawytschae* from soybean produced GA<sub>3</sub> together with both active (GA<sub>1</sub>, GA<sub>4</sub>, and GA<sub>7</sub>) and inactive (GA<sub>15</sub> and GA<sub>24</sub>) analogs [31]. Root isolates of *Penicillium citrinum* from the dune plant *Ixeris repens* [32], and *Arthrinium phaeospermum* from a sedge species (*Carex kobomugi*) [33] both produced GA<sub>1</sub>, GA<sub>3</sub>, GA<sub>4</sub>, and GA<sub>7</sub>, along with inactive forms (GA<sub>5</sub>, GA<sub>9</sub>, GA<sub>12</sub>, GA<sub>15</sub>, GA<sub>19</sub>, GA<sub>20</sub>, and GA<sub>24</sub>). Strains of *Aspergillus fumigatus*, *Cladosporium sphaerospermum* and *Talaromyces funiculosus* (= *Penicillium funiculosum*) from soybean were found to produce bioactive GAs (respectively G<sub>4</sub>, G<sub>9</sub>, and G<sub>12</sub> the former; GA<sub>3</sub>, GA<sub>4</sub>, and GA<sub>7</sub> the intermediate; GA<sub>1</sub>, GA<sub>4</sub>, GA<sub>8</sub>, and GA<sub>9</sub> the latter), besides the inactive GA<sub>5</sub>, GA<sub>15</sub>, GA<sub>19</sub>, and GA<sub>24</sub> [34–37]. Another strain of *Penicillium* sp. from crown daisy (*Chrysanthemum coronarium*) was found to promote shoot elongation due to the production of all bioactive GAs (GA<sub>1</sub>, GA<sub>3</sub>, GA<sub>4</sub>, GA<sub>7</sub>), along with a few inactive forms (GA<sub>9</sub>, GA<sub>12</sub>, GA<sub>15</sub>, GA<sub>19</sub>, GA<sub>20</sub>) [38]. Finally, GA<sub>3</sub> has been reported as a fermentation product of an unidentified endophytic strain from *Curcuma wenyujin* [39].

Cytokinins are a group of N<sup>6</sup>-substituted adenine derivatives influencing cell division, vascular development, apical dominance, stress tolerance and leaf senescence. Besides several mycorrhizal fungi reported to contribute to cytokinin levels of roots [40,41], production of these phytohormones has been well documented in the above-mentioned *P. indica*. In fact, relatively high levels of isopentenyladenine and *cis*-zeatins can be found in liquid cultures of this fungus, and accordingly the cytokinin levels are remarkably higher in roots of inoculated plants. Conversely, auxin levels are not influenced despite the ability by *P. indica* to produce this phytohormone as well, in connexion with the hypothesized conversion of some IAA into inactive compounds [42].

Finally, it must be mentioned that production of IAA, GA, abscisic acid and jasmonic acid in several combinations was observed by a pool of unidentified endophytic fungi recovered from five plants used in Indian ethnomedicine, *Camellia caduca*, *Osbeckia chinensis*, *Osbeckia stellata*, *Potentilla fulgens*, and *Schima khasiana* [43].

### 3. Compounds from Essential Oils

Essential oils of plants have a very varied chemical composition, including over 60 different kinds of volatile molecules which can be extracted by distillation and belong to two main groupings, terpenes and aromatic products. Besides contributing to the scent of plants, many of these compounds present interesting bioactive properties, ranging from antibiotic to antitumor effects [44]. The ability to produce such volatile antibiotics has stimulated to investigate several endophytic strains for their possible use in the so-called mycofumigation of foodstuffs [45–47]. Additional prospects for biotechnological applications reside in their use as flavoring agents in the food industry [48], and even as biofuels [49]. Not surprisingly, many compounds known from essential oils have been also found as secondary metabolites of endophytic fungi (Table 1), and novel molecules are more and more characterized as fermentation products of these strains, indicating their effective role in determining the mixture composition.

**Table 1.** Components \* of essential oils of plants extracted from fungal endophytic strains.

Compounds		Producing Species	Host Plants	Reference
Phenyl propanes				
Asarone		<i>Muscodor tigerii</i>	<i>Cinnamomum camphora</i>	[50]
Eugenol		<i>Annulohypoxylon stygium</i>	not specified	[51]
		<i>Alternaria</i> sp.	<i>Rosa damascaeana</i>	[52]
Monoterpenes				
Camphor		<i>Nodulisporium</i> sp.	<i>Lagerstroemia loudoni</i>	[47]
Carene		<i>Meliniomyces variabilis</i>	<i>Pinus sylvestris</i>	[53]
		<i>Nodulisporium</i> sp.	<i>L. loudoni</i>	[47]
Cineole (eucalyptol)		<i>Nodulisporium</i> sp.	<i>Persea indica</i>	[54]
			<i>L. loudoni</i>	[47]
			<i>Cassia fistula</i>	[55]
		unknown Sordariomycetes	<i>Mentha piperita</i>	[56]
Limonene		<i>Wickerhamomyces anomalus</i>	<i>Lactuca sativa</i>	[57]
		<i>Nodulisporium</i> sp.	<i>L. loudoni</i>	[47]
		<i>Nigrograna mackinnonii</i>	<i>Guazuma ulmifolia</i>	[58]
Myrcene		<i>W. anomalus</i>	<i>L. sativa</i>	[57]
		<i>Nodulisporium</i> sp.	<i>L. loudoni</i>	[47]
Ocimene		<i>W. anomalus</i>	<i>L. sativa</i>	[57]
		<i>Nodulisporium</i> sp.	<i>L. loudoni</i>	[47]
Phellandrene		<i>Muscodor fengyangensis</i>	<i>Actinidia chinensis</i> , <i>Pseudotaxus chienii</i>	[59]
		<i>Muscodor yucatanensis</i>	<i>Bursera simaruba</i>	[60]
		unidentified strains	“weed grasses”	[61]
		<i>Muscodor</i> sp.	<i>O. granulata</i>	[62]
Pinane		<i>Nodulisporium</i> sp.	<i>L. loudoni</i>	[47]
Pinene		unknown Sordariomycetes	<i>M. piperita</i>	[56]
		<i>M. variabilis</i> , <i>Phialocephala fortinii</i>	<i>P. sylvestris</i>	[53]
		<i>W. anomalus</i>	<i>L. sativa</i>	[57]
		<i>N. mackinnonii</i>	<i>G. ulmifolia</i>	[58]
Sabinanes (thujanes)	Dihydroxysabinane	<i>Phomopsis</i> sp.	<i>Camptotheca acuminata</i>	[63]
	Sabinene (thujene)	<i>Phomopsis</i> sp.	<i>Odontoglossum</i> sp.	[64]
		<i>W. anomalus</i>	<i>L. sativa</i>	[57]
		<i>Nodulisporium</i> sp.	<i>L. loudoni</i>	[47]
Terpinene, terpineol		<i>Nodulisporium</i> sp.	<i>L. loudoni</i>	[47]
		<i>N. mackinnonii</i>	<i>G. ulmifolia</i>	[58]
Diterpenes				
Abietadiene		<i>Xylaria</i> sp.	<i>Cupressus lusitanica</i>	[65]
Totarol		<i>Xylaria</i> sp.	<i>C. lusitanica</i>	[65]

Table 1. Cont.

Compounds	Producing Species	Host Plants	Reference
<b>Sesquiterpenes</b>			
Acoradiene	<i>Phomopsis</i> sp.	<i>Odontoglossum</i> sp.	[64]
Aristolene	<i>M. yucatanensis</i>	<i>B. simaruba</i>	[60]
	<i>M. yucatanensis</i>	<i>B. simaruba</i>	[60]
Aromadendrene, isodene	<i>Phoma</i> sp.	<i>Larrea tridentata</i>	[66]
	<i>Xylaria</i> sp.	<i>C. lusitanica</i>	[65]
Bisabolene	<i>M. fengyangensis</i>	<i>A. chinensis, P. chienii</i>	[59]
	<i>Xylaria</i> sp.	<i>C. lusitanica</i>	[65]
Bisabolol	<i>Muscodor kashayum</i>	<i>Aegle marmelos</i>	[67]
Cadinanes	Cadalenes, calamenenes	<i>Phomopsis cassiae</i>	<i>Cassia spectabilis</i> [68]
	Bombamalone D, calamenenes, dysodensiol	<i>Phomopsis</i> sp.	<i>Pleiblastus amarus</i> [69]
	D, indicumolide C		
	Cadinene, amorphene, muurolene	<i>Phoma</i> sp.	<i>L. tridentata</i> [66]
		<i>Xylaria</i> sp.	<i>C. lusitanica</i> [65]
	Cubenol	<i>Xylaria</i> sp.	<i>C. lusitanica</i> [65]
Carotol	<i>M. tigerii</i>	<i>C. camphora</i>	[50]
Caryophyllane	<i>Xylaria</i> sp.	<i>C. lusitanica</i>	[65]
Caryophyllene (humulene)		<i>Cinnamomum zeylanicum</i>	[45]
		<i>Muscodor albus</i>	<i>G. ulmifolia</i> [70]
		<i>M. fengyangensis</i>	<i>A. chinensis, P. chienii</i> [59]
		<i>M. yucatanensis</i>	<i>B. simaruba</i> [60]
		<i>M. variabilis, P. fortinii</i>	<i>P. sylvestris</i> [53]
		<i>Phoma</i> sp.	<i>L. tridentata</i> [66]
Isocaryophyllene	<i>Muscodor sutura</i>	<i>Prestonia trifidi</i>	[71]
Presilphiperfolanes	<i>Xylaria</i> sp.	<i>Piper aduncum</i>	[72]
Cedranes	Cedrene, cedrol	<i>Xylaria</i> sp.	<i>C. lusitanica</i> [65]
	Diepicedrene-1-oxide	<i>M. fengyangensis</i>	<i>A. chinensis, P. chienii</i> [59]
Chamigrene		<i>Phoma</i> sp.	<i>L. tridentata</i> [66]
		<i>M. sutura</i>	<i>P. trifidi</i> [71]
Cuparene	unknown Sordariomycetes	<i>M. piperita</i>	[56]
Drimanes	Albicanol	<i>Perenniporia tephropora</i>	<i>Taxus chinensis</i> var. <i>mairei</i> [73]
	Hydroxyconfertifolin	<i>Phomopsis</i> sp.	<i>Rhizophora stylosa</i> [74]
β-Elemene		<i>Nodulisporium</i> sp.	<i>Cinnamomum loureirii</i> [46]
		<i>M. yucatanensis</i>	<i>B. simaruba</i> [60]
		<i>Penicillium baarnense, Penicillium frequentans</i>	<i>Curcuma zedoaria</i> [75]

Table 1. Cont.

Compounds	Producing Species	Host Plants	Reference
Eremophilanes	Eremophilanolides	<i>Xylaria</i> sp.	<i>Licuala spinosa</i> [76]
	Isopetasols	unidentified strain	<i>Picea rubens</i> [77]
	Mairetolide A	<i>Xylaria</i> sp.	<i>C. lusitanica</i> [78]
	Mairetolide F	<i>Xylaria</i> sp.	<i>L. spinosa</i> [76]
	Valencene	<i>C. zeylanicum</i>	[45]
		unidentified vine plant	[79]
		<i>Oryza granulata</i>	[62]
Eudesmanes, eudesmenes (selinenes)	<i>Xylaria</i> sp.	<i>C. lusitanica</i>	[78]
	<i>Eutypella</i> sp.	<i>Etlingera littoralis</i>	[80]
	<i>Nodulisporium</i> sp.	<i>C. loureirii</i>	[46]
	<i>Phoma</i> sp.	<i>L. tridentata</i>	[66]
	<i>Xylaria</i> sp.	<i>C. lusitanica</i>	[65]
Arundinols, arundinones	<i>Microsphaeropsis arundinis</i>	<i>Ulmus macrocarpa</i>	[81]
Capitulatin B, hydroxycapitulatin B	<i>Nigrospora oryzae</i>	<i>Aquilaria sinensis</i>	[82]
Farnesene	<i>Xylaria</i> sp.	<i>C. lusitanica</i>	[65]
Guaianes: guaiene, guaial (champacol), aciphyllene, bulnesene, gurjunene	<i>M. albus</i>	unidentified vine plant	[79]
		<i>C. zeylanicum</i>	[45]
		<i>Myristica fragrans</i>	[83]
	<i>Phoma</i> sp.	<i>G. ulmifolia</i>	[70]
		<i>L. tridentata</i>	[66]
Himachalene	<i>Xylaria</i> sp.	<i>C. lusitanica</i>	[65]
Irones	<i>Phoma</i> sp.	<i>L. tridentata</i>	[66]
Longicyclene	<i>Rhizopus oryzae</i>	<i>Iris germanica</i>	[84]
Longifolenes	<i>M. variabilis, P. fortinii</i>	<i>P. sylvestris</i>	[53]
	<i>M. yucatanensis</i>	<i>B. simaruba</i>	[60]
	<i>P. fortinii</i>	<i>P. sylvestris</i>	[53]
Longipinene	<i>Xylaria</i> sp.	<i>C. lusitanica</i>	[65]
Occidentalol	<i>Phoma</i> sp.	<i>L. tridentata</i>	[66]
Thujopsanol, thujopsene	<i>Xylaria</i> sp.	<i>C. lusitanica</i>	[65]
	<i>M. sutura</i>	<i>P. trifidi</i>	[71]
Ylangene	<i>Phoma</i> sp.	<i>L. tridentata</i>	[66]
Zingiberene	<i>Xylaria</i> sp.	<i>C. lusitanica</i>	[65]

\* Not including fatty acids and their methyl esters.

Within the several groups of sesquiterpenes occurring in essential oils, the eremophilanes are particularly widespread among endophytic fungi, and many novel molecules of this series have been first discovered as their fermentation products (Table 2). It is quite interesting to note that eremophilanes include compounds with phytotoxic effects, such as phaseolinone and phomenone which are also known from an endophytic strain of *Xylaria* sp. from the matico tree (*Piper aduncum*) [72].

**Table 2.** Eremophilane compounds first characterized from endophytic fungal strains.

Compounds	Producing Species	Host Plants	Reference
Botryosphaeridione	<i>Phoma</i> sp.	<i>Melia azedarach</i>	[85]
Cupressolides A-B	<i>Xylaria</i> sp.	<i>Cupressus lusitanica</i>	[78]
Dihydroberkleasmin A	<i>Pestalotiopsis photinae</i>	<i>Podocarpus macrophyllus</i>	[86]
Eremoxylarins A-B	xylariaceous fungus	not specified	[87]
MBJ-0011-13	<i>Apiognomonina</i> sp.	not specified	[88]
Periconianone B	<i>Periconia</i> sp.	<i>Annona muricata</i>	[89]
Pestalotiopsin A-B	<i>P. photinae</i>	<i>P. macrophyllus</i>	[90]
Phomadecalins	<i>Microdiplodia</i> sp.	<i>Pinus</i> sp.	[91]
unnamed compounds	<i>Xylaria</i> sp.	<i>Licuala spinosa</i>	[76]
	<i>Xylaria</i> sp.	mangrove plant	[92]
Xylarenones	<i>Xylaria</i> sp.	<i>Torreya jackii</i>	[93]
	<i>Camarops</i> sp	<i>Alibertia macrophylla</i>	[94,95]

Data introduced in the above tables are eventually incomplete, due to the ongoing addition of novel findings concerning the direct and indirect influence of endophytic fungi on the composition of essential oils, and ensuing effects on their biological activities. The resulting complex framework and the intriguing applicative perspectives are possibly indicative of the opportunity of a dedicated review for such a hot research topic. A recent one that can be cited here [96] is limited to sesquiterpenes, and not specifically addressed to fungal endophytes.

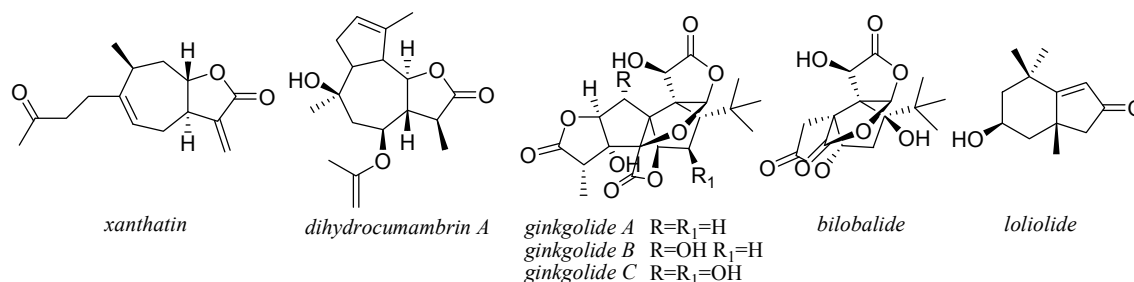
Another interesting finding on terpenoids from essential oils concerns a few such compounds, namely aristolene, guaiane and thujopsene, produced by strains of *Daldinia* spp. establishing symbiotic relationships with *Xiphydria* woodwasps on a number of tree species [97]. In a strict sense, these fungi cannot be considered endophytic since they are inoculated by the wasps and colonize the galleries excavated by their larvae. However, their belonging to the Xylariaceae, a group including *Xylaria*, *Hypoxylon*, *Muscodora* and *Nodulisporium* which are well-known for their endophytic habit, stimulates the appraisal of the ecological role held by these compounds in the identification of the host plant and the establishment of this particular symbiotic relationship, and to consider their possible relevance in other plant-insect interactions.

Finally, the effect of endophytic fungal strains in modifying the pattern of compounds in the essential oils of plants may have intriguing interactions with crop resistance/susceptibility toward pests. As an example, it has been observed that tomato plants harboring an unspecialized endophyte (*Acremonium strictum*), which remarkably influences composition of volatile compounds released by the host, are significantly preferred by adult whiteflies (*Trialeurodes vaporariorum*) [98], and for oviposition by the cotton bollworm (*Helicoverpa armigera*) [99]. Therefore, any factors influencing composition of essential oils may be considered in view of enhancing plant protection.

#### 4. Other Terpenoids

Sesquiterpene lactones present some affinity with a few analog components of essential oils, such as guaianes and eudesmanes. Within this category, loliolide (Figure 1), first characterized from *Lolium perenne* [100], has been reported from a strain of *Annulohypoxylon ilanense* from the wood of

a plant of *Cinnamomum* sp. [101]. Xanthatin (Figure 1), first isolated from cockleburs (*Xanthium* spp.) and characterized for its antimicrobial, anti-inflammatory, pro-apoptotic and trypanocidal properties [102,103], has been recovered from cultures of a strain of *Paecilomyces* sp. from *Panax ginseng* [104]. Moreover, dihydrocumambrin A (Figure 1), known as a secondary metabolite of *Glebionis coronaria* (= *Chrysanthemum coronarium*), has been recently extracted as a fermentation product of a strain of *Lasiodiplodia* (= *Botryodiplodia*) *theobromae* endophytic in leaves of *Dracaena draco* [105].



**Figure 1.** Structures of some terpenoids produced by endophytic fungi.

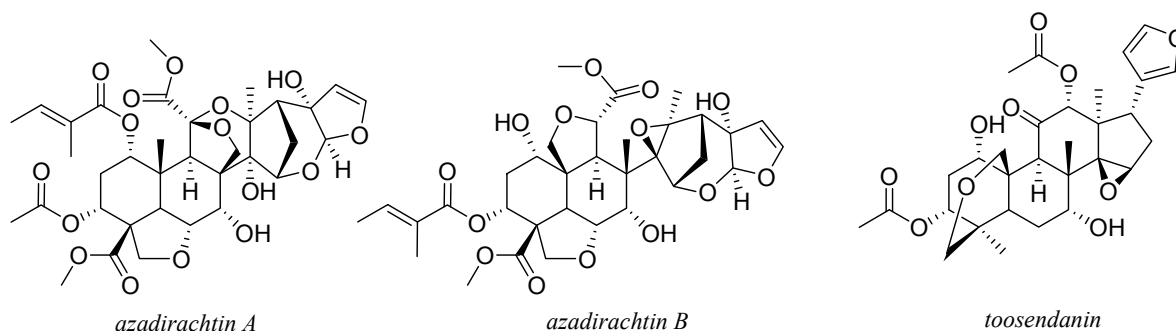
Ginkgolides are diterpenoid lactones known as secondary metabolites of *G. biloba* which are considered, particularly ginkgolide B, as prospect drugs based on documented antagonistic effects against the platelet-activating factor involved in a number of inflammatory disorders. Ginkgolides A-C and the related compound bilobalide (Figure 1) have been found as fermentation products of an endophytic strain of *Fusarium oxysporum* recovered from root bark of this living fossil tree [106].

More terpenoid compounds can be found in oleoresins of certain plants. Agathic acid is a diterpenoid representing the major component of the oleoresin of *Agathis microstachya*, an endangered species belonging to the Araucariaceae endemic to Queensland (Australia) [107], and more recently found in oleoresin of copaiba (*Copaifera* spp.) in the Amazon region [108]. It has been extracted from cultures of a strain of *Botryosphaeria* sp. endophytic in leaves of *Maytenus hookeri*, together with the related isocupressic acid which is commonly found in the needles of several coniferous species [109]. These compounds have been reported for an abortive effect on cows [110], while agathic acid is also known for some extent of trypanocidal activity [108].

Limonoids are tetranortriterpenes reported from members of Rutaceae and Meliaceae, among which the azadirachtins are best known and exploited for their insecticidal properties [111]. Azadirachtins A and B (Figure 2) have been recently extracted from cultures of a strain of *Penicillium* (*Eupenicillium*) *parvum* endophytic in the neem plant (*Azadirachta indica*) [112]. However, the importance of endophytes in the biosynthesis of these plant products may be more substantial, considering that an endophytic *Penicillium* strain from the chinaberry tree (*Melia azedarach*), which is another source of azadirachtin, has been reported to produce the austins [113], a series of meroterpenoids which may share the same biosynthetic pathway.

The structurally-related toosendanin (Figure 2) extracted from fruits and bark of *Melia toosendan*, possibly a synonym of *M. azedarach* which is used as an anti-helminthic remedy in the Chinese traditional medicine, has been also characterized with reference to its insecticidal effects deriving from antifeedant and growth regulatory properties [111]. Three unidentified strains endophytic in

*M. azedarach* have been found to produce this compound [114], whose possible exploitation as an antitumor drug has been recently envisaged [115].



**Figure 2.** Structures of azadirachtins and toosendanin.

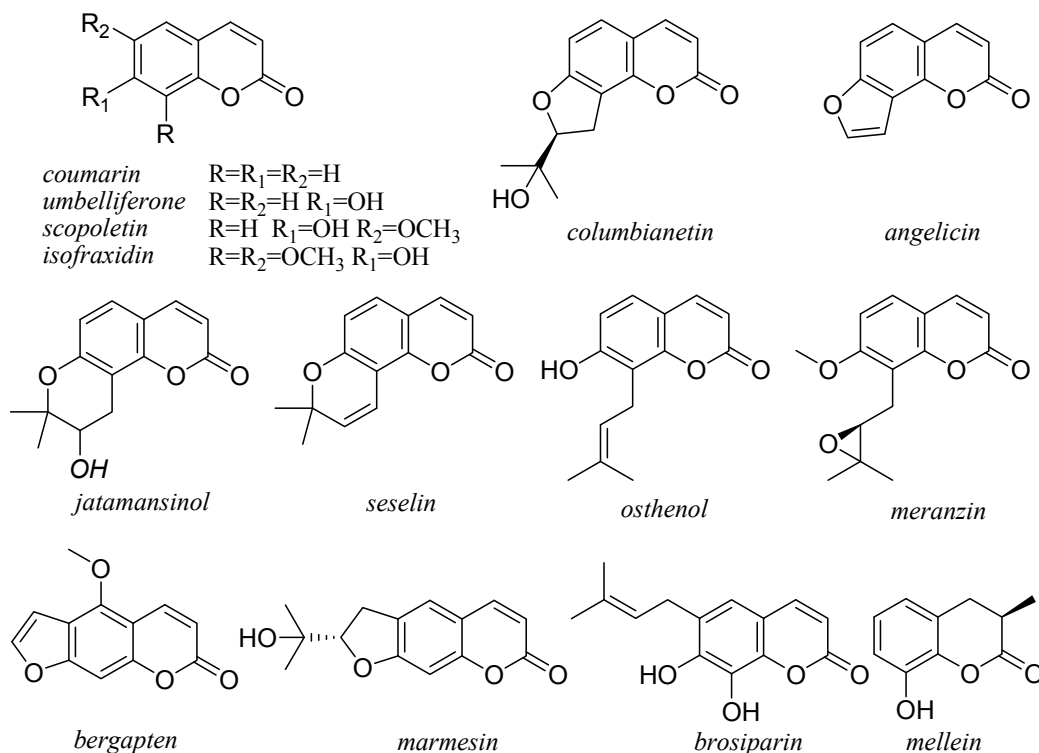
## 5. Coumarins

Additional metabolites occasionally found in essential oils, such as bergapten, can be ascribed to the coumarins, a heterogeneous class of natural products whose molecular structure is based on a benzopyran-2-one (Figure 3). These compounds are widespread in edible plants, therefore commonly assumed through dietary exposure, and considered interesting prospects for a pharmaceutical exploitation due to their antioxidant, anti-inflammatory, anticoagulant, antimicrobial, anticancer, antihypertensive, antihyperglycemic, and neuroprotective properties [116,117]. A number of these compounds primarily known from plants have recently started being reported as metabolites of endophytic fungi, such as coumarin found in extracts of strains of *Alternaria* spp., *Penicillium* spp. and *Aspergillus flavus* from the annual herb *Crotalaria pallida* [118].

Scopoletin (6-methoxy-7-hydroxycoumarin) is reported from several plants, where it is possibly involved in protection against pathogens due to its antimicrobial properties [119]. This compound has been isolated from a mangrove endophytic strain of *Penicillium* sp., together with bergapten and umbelliferone (7-hydroxycoumarin) [120]. Scopoletin, umbelliferone and 7-*O*-prenylumbelliferone, along with additional coumarins known from several plant species such as angelicin, brosiparin, columbianetin, jatamansinol, osthenol and seselin, have been recently extracted from cultures of an endophytic strain of *A. ilanense* [121]. Moreover, marmesin has been reported from a mangrovia endophytic strain of *Fusarium* sp. [122], while bergapten and meranzin have been extracted as fermentation products of a previously-mentioned isolate of *L. theobromae* from *D. draco* [105].

Within dihydroisocoumarins, mellein derives its name by a strain of *Aspergillus melleus* from which it was first characterized [123]. It is quite a common fungal metabolite, together with a number of derivatives [124]. However, several products in this series have been also directly reported from plants [125,126]. Examples of compounds produced by both plants and endophytic strains include 7-hydroxymellein extracted from cultures of a strain of *Penicillium* sp. associated to *Alibertia macrophylla* [127] and a strain of *Xylaria cubensis* derived from leaves of *Litsea akoensis* [128], and mellein itself from a strain of *Nigrospora* sp. from the benzoil tree (*Moringa oleifera*) [129]. Another xylariaceous fungus from fruits of the wingleaf soapberry (*Sapindus saponaria*) [130], and a strain of *Annulohypoxyton squamulosum* from *Cinnamomum* sp. [131]

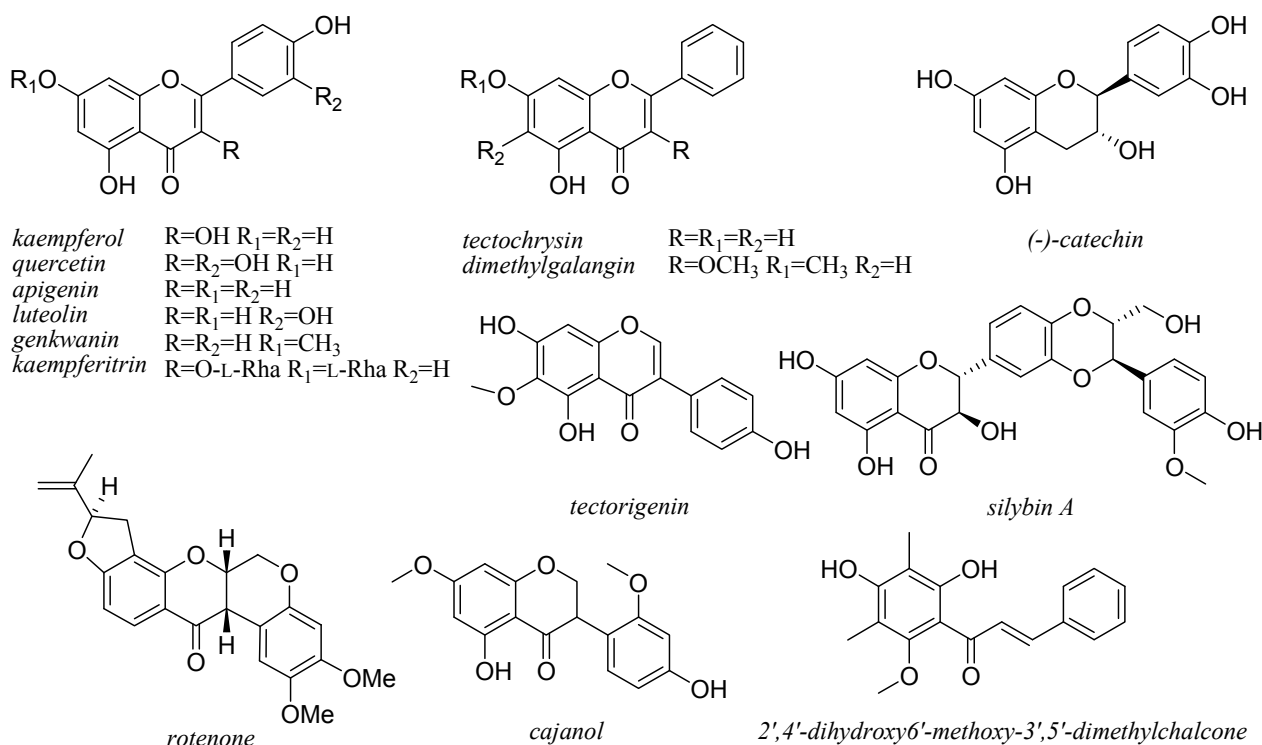
produced both compounds. Finally, a few mellein derivatives have been found together with isofraxidin (7-hydroxy-6,8-dimethoxycoumarin) as fermentation products of an endophytic strain of *Annulohypoxylon bovei* var. *microspora* from bark of *Cinnamomum* sp. [132].



**Figure 3.** Structures of coumarins produced by endophytic fungi.

## 6. Flavonoids

Commonly associated to coumarins for their fundamental antioxidant properties, flavonoids also display consistent anti-inflammatory, antibacterial, antiviral, antitumor, and vasodilatory effects [133]. These polyphenolic compounds are widespread in plants where they represent a biochemical mechanism in pre- and post-infection resistance against pathogens [134]. Their structure consists of two benzene rings at either side of a 3-carbon ring, and multiple substitutions in this fundamental frame originate several classes of derivatives, such as flavones, isoflavones, flavonols, flavanones, catechins, and anthocyanins (Figure 4). Such a variation, and the concomitant occurrence of several compounds belonging to this class is the reason why many reports dealing with their production by endophytic fungal strains consider the total flavonoid content rather than every single product [135,136]. When a more detailed analysis is carried out, a complex pattern of metabolites in this series results; this is the case of a strain of *A. ilanense* producing kaempferol, quercetin, genkwanin, (+/−)-catechin, (−)-4'-hydroxy-5,7,3'-trimethoxyflavan-3-ol, tectochrysin (5-hydroxy-7-methoxyflavone), dimethylgalangin (3,7-dimethoxy-5-hydroxyflavone), and 5-hydroxy-3,6,7-trimethoxyflavone [121], and a strain of *Fusarium* sp. producing tectorigenin (6-methoxy-5,7,4'-trihydroxyisoflavone) and a few more isoflavones [122].



**Figure 4.** Structures of flavonoids produced by endophytic fungi.

Kaempferol has been more frequently mentioned as a fermentation product of endophytic fungi, such as a strain of *Mucor fragilis* from rhizomes of *Sinopodophyllum hexandrum* [137], a strain of *Fusarium chlamydosporum* from stem of *Tylophora indica* (Asclepiadaceae) [138], and a previously-mentioned unidentified strain from *C. wenyujin* [39]. It has been also found together with quercetin in the above-mentioned strain of *A. squamulosum* [131], and in a strain of *A. bovei* var. *microspora* together with kaempferitrin and luteolin [139]. A widespread plant metabolite with putative cancer chemopreventive and therapeutic properties [140], luteolin has been also reported as a secondary metabolite of an endophytic strain of *A. fumigatus* from the pigeon pea (*Cajanus cajan*), which itself is known as a source of this phytoestrogen [141].

Cajanol is another isoflavone from roots of *C. cajan* displaying antimicrobial properties, and pro-apoptotic activity resulting in assays against human breast cancer cells [142]. Endophytic strains of *Hypocrea lixii* from roots of *C. cajan* have also been reported to produce this compound in liquid cultures [143]. Another endophytic fungus from *C. cajan*, *Chaetomium globosum*, has been reported to produce apigenin (4',5,7-trihydroxyflavone) [144]. Its glycosidic derivative vitexin (apigenin-8-C-β-D-glucopyranoside) has been found as a fermentation product of a strain of *Colletotrichum* sp. endophytic in *G. biloba* [145]. More glycosidic derivatives, namely apigenin-5-O-α-L-rhamnopyranosyl-(1→3)-β-D-glucopyranoside and euryanoside (apigenin-5-O-α-L-rhamnopyranosyl-(1→2)-(6"-O-acetyl)-β-D-glucopyranoside), have been detected as transformation products by a strain of *Paraconiothyrium variabile* endophytic in the Japanese plum yew (*Cephalotaxus harringtonii*) growing on crude extracts of the same plant, by which these compounds had been previously reported [146].

Rotenone is one of the oldest known bioactive plant metabolites, extracted from roots of tropical Leguminosae such as *Lonchocarpus* spp., *Tephrosia* spp., *Mundulea* spp., *Dalbergia paniculata* and

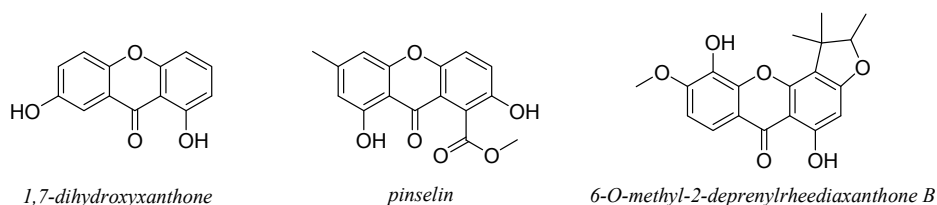
*Derris elliptica* [147]. An unidentified *Penicillium* strain from the latter plant has been reported to produce this compound or a structural analog [148].

Silymarin is a bioactive extract of the fruits of milk thistle (*Silybum marianum*), containing seven flavolignans with reported antitumor and hepatoprotective properties [149,150]. Three of these compounds, silybin A, silybin B, and isosilybin A have been extracted as fermentation products of a strain of *Aspergillus iizukae* isolated from the leaves of *S. marianum*. Interestingly, flavonolignan synthesis attenuated after repeated subculturing of this strain, but could be resumed when autoclaved leaves of the host plant were added to the growth medium [151].

The chalcones (benzalacetophenones) are involved in flavonoid biosynthesis in plants through an isomerization process promoted by the enzyme chalcone flavanone isomerase [152]. These compounds exhibit notable bioactive properties [153], and significant anti-cancer effects [154]. An endophytic strain of *Ceriporia lacerata* has been found to produce 2',4'-dihydroxy-6'-methoxy-3',5'-dimethylchalcone first extracted from its host plant *Cleistocalyx operculatus* (= *Eugenia operculata* or *Syzygium operculatum*) [155].

## 7. Xanthenes and Quinones

With a number of pharmaceutical applications, xanthenes (Figure 5) are structurally related to flavanoids, and also commonly recovered from both plant and fungal sources [156]. With reference to endophytic fungi, a mangrovia strain of *Penicillium* sp. has been found to produce 1,7-dihydroxyxanthone [120], primarily known for its antimalarial properties and reported as a secondary metabolite of plants such as *Weddellina squamulosa* (Podostemaceae) and several species in the Guttiferae [157,158].



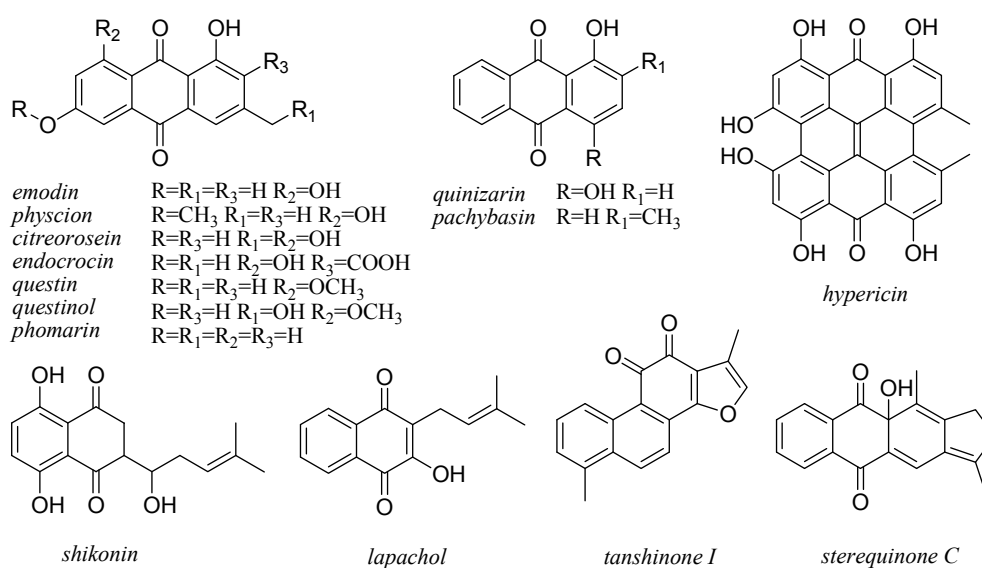
**Figure 5.** Structures of xanthenes produced by endophytic fungi.

Pinselin was initially characterized from a strain of *Penicillium amarum*, but later found to be identical to cassiollin reported from *Cassia occidentalis* [159]. This metabolite has been found as a fermentation product of a strain of *Phomopsis* sp. endophytic in rhizome of *Paris polyphylla* var. *yunnanensis* [160], together with additional xanthenes including 6-O-methyl-2-deprenylrheediaxanthone B, previously extracted from bark of *Garcinia vieillardii* [161].

Fairly widespread as plant metabolites and widely used as dyes in the textile industry, anthraquinones are believed to contribute to the defense against pests and disease agents, based on their antifungal, antibacterial and insecticidal properties [162]. Several compounds in this class are also known from endophytic fungi (Figure 6). Emodin, physcion and citreorosein, found in several plant species such as rhubarb (*Rheum* spp.) [163], *Cassia* spp. [164], and *Polygonum cuspidatum* [165,166], are also produced by heterologous endophytic strains of *Penicillium* spp. (e.g., *P. herquei*, *P. janthinellum*) [167–169]. Emodin has been also reported from a strain of *Talaromyces* sp. from the

mangrove *Kandelia candel* [170], while physcion was also extracted from cultures of an unidentified strain from the mangrove *Avicennia marina* [171], and of strains of *A. fumigatus* from *Cynodon dactylon* [172], and *Aspergillus terreus* from *Opuntia ficus-indica* [173]. Quinizarin known from roots of the madder plant (*Rubia tinctorum*) [174], has been reported as a secondary metabolite of a previously-mentioned unidentified strain from *C. wenyujin* [39]. Endocrocin, reported from roots of *Rumex nepalensis* [175], has recently been found to be produced by an endophytic strain of *Pestalotia (Pestalotiopsis) acaciae* [176]. Questinol and questin are known from *Polygonum* spp. [177] and again from *Cassia* spp. [164]. The former compound has been detected in the culture extracts of strains of *Eurotium rubrum* from the mangrove *Hibiscus tiliaceus* [178] and *P. glabrum* from pomegranate fruits [19], while the latter has been reported as a metabolite of an unidentified strain belonging to the Dothideomycetes from the Thai medicinal plant *Leea rubra*. This strain also produces the biosynthetically related chromone derivative eugenitin, previously extracted as a secondary metabolite of clove (*Syzygium aromaticum*), and its analog 6-hydroxymethyleugenitin [179]. A strain of *Phoma sorghina* endophytic in the medicinal plant *Tithonia diversifolia* [180] has been found to produce pachybasin and phomarin, known as secondary metabolites of species in the Scrophulariaceae, such as *Digitalis* spp. [181] and *Isoplexis isabelliana* [182], and 1,7-dihydroxy-3-methylanthraquinone, first extracted from leaves of *Digitalis viridiflora* [183]. Once again, the three latter compounds have been more recently extracted from cultures of a strain of *Coniothyrium* sp. endophytic in *Salsola oppositifolia* [184]. Finally, pachybasin has been also reported from an unidentified strain from the yellow moonshed (*Arcangelisia flava*) [185].

Hypericin, a secondary metabolite of St. John's wort (*Hypericum perforatum*) and other congeneric species, has been extensively studied for its antidepressant, antiviral and antitumor properties. In combination with light the compound effectively induces apoptosis and/or necrosis of cancer cells, the reason why it has been exploited for the photodynamic therapy of cancer [186]. Hypericin has been found as a metabolic product of an endophytic strain of *Thielavia subthermophila* isolated from *H. perforatum* in India, together with the above-mentioned emodin considered as a possible precursor [187,188].



**Figure 6.** Structures of anthraquinones produced by endophytic fungi.

Sterequinone C, primarily extracted from bark of the Ayurvedic medicinal plant *Stereospermum personatum* [189], has been more recently found as a metabolite of an unidentified strain of *Penicillium* sp. from leaf of the mangrove *Avicennia* [120].

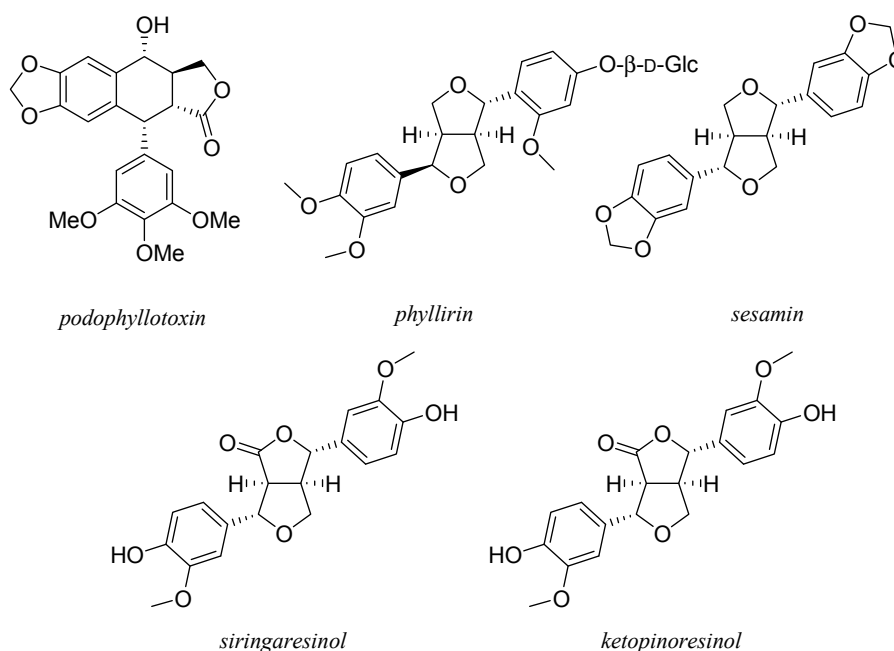
The tanshinones are diterpenoid quinones from roots and rhizomes of danshen (*Salvia miltiorrhiza*) and other *Salvia* spp. exerting antioxidant, anti-inflammatory and antitumor effects [190]. These compounds have been also extracted from endophytic strains of the same plant, particularly TR21 of *Emericella foeniculicola* [191], and D16 of *Trichoderma atroviride* [192]. Polysaccharides from the mycelium of the latter strain were found to elicit root growth and tanshinone production [193]. Moreover, a previously-mentioned strain of *Paecilomyces* sp. from *P. ginseng* has been found to produce isotanshinone [104].

Shikonin is a pigment of the Chinese therapeutic herb zicao (*Lithospermum erythrorhizon*) with a naphthoquinone structure, displaying interesting pharmacological activities based on its anti-inflammatory, antigonadotropic, anti-HIV and antitumor properties [194]. This compound has been recently recovered from extracts of an endophytic strain from roots of the old lady cactus (*Mammillaria hahniana*) [195]. Lapachol is another naphthoquinone derivative originally extracted from the bark of the lapacho tree (*Handroanthus impetiginosus*, syn. *Tabebuia avellanedae*), but later found in plants belonging to different botanical families. It is an active principle in lapacho used in ethnomedicine by indigenous populations of South America, and reported for a wide range of pharmacological activities [196]. Endophytic strains of *Alternaria* sp., *A. alternata*, *A. niger* and *Penicillium* sp. from the silver trumpet tree (*Tabebuia argentea*) have been found to produce this compound [197,198].

## 8. Lignans

Quite widespread as plant metabolites [199], the podophyllotoxins and related cyclolignans have been also characterized for their insecticidal effects [200,201]. However, the higher reputation for podophyllotoxin (Figure 7) and a few synthetic derivatives relies on their pharmacological applications, particularly as antitumor drugs [199,202]. These products have also been reported from an increasing number of endophytic fungi, such as *Alternaria* sp. from *S. hexandrum* [203] and *Juniperus communis* (= *J. vulgaris*) [204], *Penicillium* spp. from *S. hexandrum*, *Diphylleia sinensis* and *Dyosma veitchii* [203], *Phialocephala fortinii* from *Podophyllum peltatum* [205], *Trametes hirsuta*, *Fusarium solani* and *M. fragilis* from *S. hexandrum* [137,206,207], and *F. oxysporum* from *Juniperus recurva* [208]. Moreover, deoxypodophyllotoxin has been reported from a strain of *A. fumigatus* endophytic in *J. communis* [209].

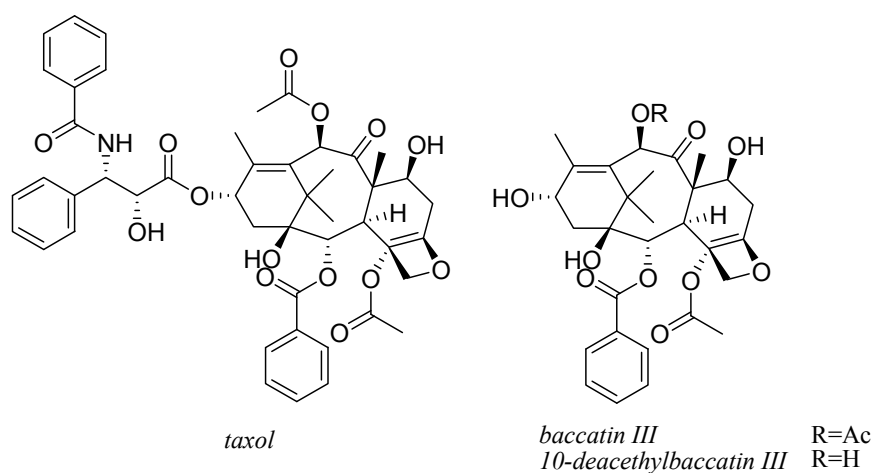
Phillyrin (Figure 7) is another lignan displaying antioxidant, anti-inflammatory and antipyretic activities, known from *Phyllirea* and a number of medicinal plants such as *Forsythia suspensa*, a shrub used in Chinese traditional medicine [210]. An endophytic strain of *Colletotrichum gloeosporioides* from a fruit of this plant was found to produce phillyrin in liquid cultures [211]. Other lignans known from several plant species, such as sesamin, syringaresinol and ketopinoresinol (Figure 7), have been recently found as secondary metabolites of an endophytic strain of *A. ilanense* [121].



**Figure 7.** Structures of lignans produced by endophytic fungi.

## 9. Taxol and Taxanes

Taxol, also known as paclitaxel, is probably the most valuable compound in this review, at least considering its notoriety as the first billion-dollar anticancer drug. Temporarily set aside in chapter 4 concerning terpenoids, this diterpene compound presenting an unusual oxytane ring and a tricyclic core (Figure 8) was originally characterized from bark of the Pacific yew (*Taxus brevifolia*) [212], but later found in all other yew species [213]. Problems for an adequate pharmaceutical supplying were soon evident, and the need to find alternative sources lead to the discovery of the first endophytic fungal strain able to synthesize this compound, isolated from the inner bark of *T. brevifolia* and ascribed to the novel species *Taxomyces andreanae* [214]. This discovery was followed by an ongoing series of similar findings from yews, but also from other plants species, attaining to a provisional number of almost 100 reports of endophytic strains belonging to 72 fungal species from 32 different host plants, as listed in Table 3. However, these figures are underestimated, considering that we have not been able to check a number of reports from China and other Asian countries. Whether or not one or more of such strains can be effectively employed by the pharmaceutical industry is still under debate [1,215], and treating this theme goes beyond the scopes of this review. Nevertheless, there is no doubt that the issue of taxol production by endophytic fungi has stimulated a wide research activity concerning drugs and other reputed bioactive compounds extracted from plants, introducing new insights in the appreciation of the microbial component of biodiversity and the opportunity of its exploitation for human wellness.



**Figure 8.** Structures of taxol and baccatins.

**Table 3.** Endophytic fungi reported for production of taxol.

Species	Host plants	Reference
<i>Acremonium</i> sp.	<i>Taxus globosa</i>	[216]
	<i>Taxus cuspidata</i>	[217]
<i>Alternaria</i> sp.	<i>Ginkgo biloba</i>	[218]
	<i>Corylus avellana</i>	[219]
<i>Aspergillus candidus</i>	<i>Taxus × media</i>	[220]
<i>Aspergillus fumigatus</i>	<i>Podocarpus</i> sp.	[221]
<i>Aspergillus niger</i> var. <i>taxi</i>	<i>T. cuspidata</i>	[222]
<i>Aspergillus</i> sp.	<i>Taxus chinensis</i>	[223]
<i>Bartalinia robillardoides</i>	<i>Aegle marmelos</i>	[224]
<i>Botryosphaeria</i> sp.	<i>T. globosa</i>	[216]
	<i>T. chinensis</i> var. <i>mairei</i>	[225]
<i>Botrytis</i> sp.	<i>T. cuspidata</i>	[226]
<i>Ceratobasidium</i> sp.	<i>T. chinensis</i>	[223]
<i>Chaetomella raphigera</i>	<i>Terminalia arjuna</i>	[227]
<i>Cladosporium cladosporioides</i>	<i>T. media</i>	[228]
<i>Cladosporium oxysporum</i>	<i>Moringa oleifera</i>	[229]
<i>Cladosporium tenuissimum</i>	<i>T. chinensis</i>	[223]
	<i>Justicia gendarussa</i>	[230]
	<i>Plumeria acutifolia</i>	[231]
<i>Colletotrichum gloeosporioides</i>	<i>T. media</i>	[232]
	<i>Tectona grandis</i>	[233]
	<i>M. oleifera</i>	[234]
<i>Colletotrichum</i> sp.	<i>Maguireothamnus speciosus</i>	[235]
<i>Coniothyrium diplodiella</i>	<i>T. chinensis</i>	[223]
<i>Didymostilbe</i> sp.	<i>T. chinensis</i> var. <i>mairei</i>	[236]
<i>Ectostroma</i> sp.	<i>T. chinensis</i> var. <i>mairei</i>	[225]
<i>Epacris</i> sp.	<i>T. chinensis</i>	[223]
<i>Fusarium arthrosporioides</i>	<i>T. cuspidata</i>	[237]

Table 3. Cont.

Species	Host plants	Reference
<i>Fusarium lateritium</i>	<i>Taxus baccata</i>	[217]
<i>Fusarium mairei</i>	<i>T. chinensis</i> var. <i>mairei</i>	[238]
<i>Fusarium oxysporum</i>	<i>Rhizophora annamalayana</i>	[239]
<i>Fusarium proliferatum</i>	<i>T. media</i>	[232]
<i>Fusarium redolens</i>	<i>Taxus wallichiana</i>	[240]
<i>Fusarium solani</i>	<i>Taxus celebica</i>	[241]
	<i>T. chinensis</i>	[242]
<i>Fusarium</i> sp.	<i>T. wallichiana</i>	[243]
	<i>T. globosa</i>	[216]
<i>Gliocladium</i> sp.	<i>T. baccata</i>	[244]
<i>Guignardia mangiferae</i>	<i>T. media</i>	[232]
<i>Gyromitra</i> sp.	<i>T. globosa</i>	[216]
<i>Lasiodiplodia theobromae</i>	<i>Morinda citrifolia</i>	[245]
	<i>T. baccata</i>	[246]
<i>Metarhizium anisopliae</i>	<i>T. chinensis</i>	[223]
<i>Monochaetia</i> sp.	<i>T. baccata</i>	[217]
<i>Mucor rouxianus</i>	<i>T. chinensis</i>	[247]
<i>Mucor</i> sp.	<i>T. chinensis</i> var. <i>mairei</i>	[248]
<i>Nigrospora</i> sp.	<i>T. globosa</i>	[216]
<i>Nodulisporium sylviforme</i>	<i>T. cuspidata</i>	[249]
<i>Ozonium</i> sp.	<i>T. chinensis</i> var. <i>mairei</i>	[250]
<i>Paraconiothyrium brasiliense</i>	<i>T. chinensis</i>	[223]
<i>Paraconiothyrium</i> sp.	<i>T. media</i>	[251]
<i>Penicillium aurantiogriseum</i>	<i>C. avellana</i>	[252]
<i>Penicillium raistrickii</i>	<i>Taxus brevifolia</i>	[253]
<i>Penicillium</i> sp.	<i>Taxus yunnanensis</i> (= <i>T. wallichiana</i> )	[254]
	<i>T. globosa</i>	[216]
	<i>T. chinensis</i>	[255]
<i>Periconia</i> sp.	<i>Torreya grandifolia</i>	[256]
<i>Pestalotia bicilia</i>	<i>T. baccata</i>	[217]
<i>Pestalotia pauciseta</i>	<i>Cardiospermum helicacabum</i>	[257]
	<i>Tabebuia pentaphylla</i>	[258]
<i>Pestalotiopsis guepinii</i>	<i>Wollemia nobilis</i>	[259]
<i>Pestalotiopsis microspora</i>	<i>T. cuspidata</i> , <i>T. wallichiana</i>	[260]
	<i>Taxodium distichum</i>	[261]
<i>Pestalotiopsis neglecta</i>	<i>T. cuspidata</i>	[262]
<i>Pestalotiopsis</i> sp.	<i>W. nobilis</i>	[259]
	<i>Catharanthus roseus</i>	[263]
<i>Pestalotiopsis terminaliae</i>	<i>T. arjuna</i>	[264]
<i>Pestalotiopsis versicolor</i>	<i>T. cuspidata</i>	[262]
<i>Pezicula</i> sp.	<i>T. chinensis</i>	[223]
<i>Phoma betae</i>	<i>G. biloba</i>	[265]

Table 3. Cont.

Species	Host plants	Reference
<i>Phomopsis</i> sp.	<i>G. biloba</i> , <i>Larix leptolepis</i> , <i>T. cuspidata</i>	[266]
	<i>T. chinensis</i>	[223]
<i>Phyllosticta melochiae</i>	<i>Melochia corchorifolia</i>	[267]
<i>Phyllosticta</i> sp.	<i>Ocimum basilicum</i>	[268]
<i>Phyllosticta spinarum</i>	<i>Cupressus</i> sp.	[269]
<i>Pithomyces</i> sp.	<i>Taxus sumatrana</i>	[216]
<i>Rhizopus</i> sp.	<i>T. media</i>	[270]
<i>Seimatoantlerium nepalense</i>	<i>T. wallichiana</i>	[271]
<i>Sordaria</i> sp.	<i>T. chinensis</i>	[223]
<i>Sporormia minima</i>	<i>T. wallichiana</i>	[272]
<i>Stegolerium kukenani</i>	<i>Stegolepis guianensis</i>	[273]
<i>Stemphylium sedicola</i>	<i>T. baccata</i>	[274]
<i>Taxomyces andreanae</i>	<i>T. brevifolia</i>	[214]
<i>Taxomyces</i> sp.	<i>Taxus</i> sp.	[275]
<i>Trichoderma</i> sp.	<i>T. chinensis</i>	[223]
<i>Trichothecium</i> sp.	<i>T. wallichiana</i>	[272]
<i>Tubercularia</i> sp.	<i>T. mairei</i>	[276]
<i>Xylaria</i> sp.	<i>M. speciosus</i>	[235]
	<i>T. chinensis</i>	[223]

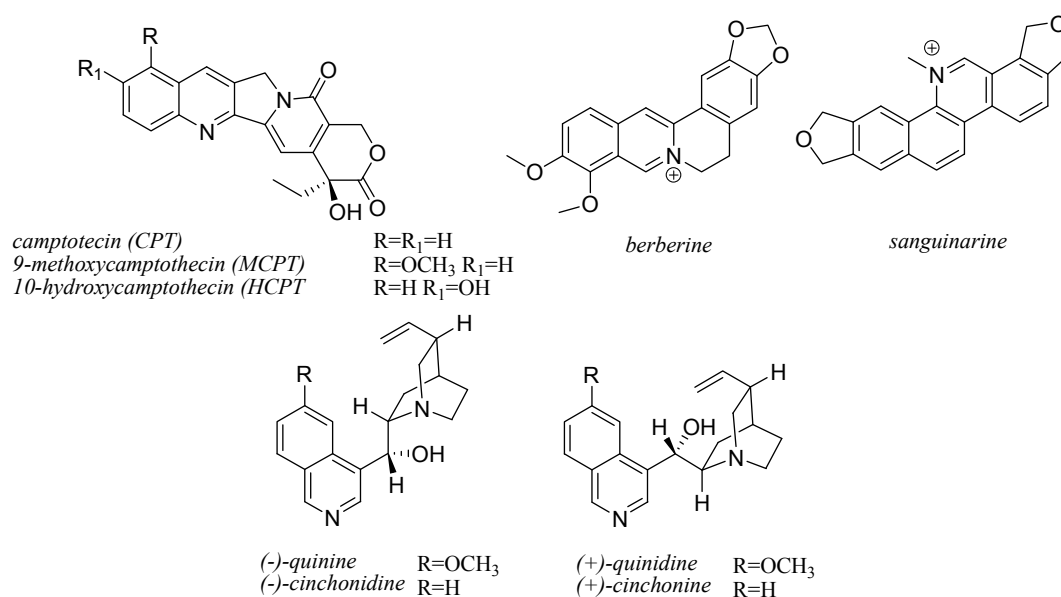
Another opportunity to obtain taxol is represented by a semisynthetic method starting from the structurally related taxane compounds baccatin III and 10-deacetylbaccatin III (Figure 8), which are more easily accessible for their occurrence in yew needles [277]. Besides a number of papers where these precursors are reported together with taxol (Table 3), specific references consider their production by endophytic strains from *Taxus wallichiana*, respectively *Diaporthe phaseolorum* [278] and *Trichoderma* sp. [279]. A more general biosynthetic ability concerning taxanes has been evidenced in a number of endophytic strains isolated from *Taxus baccata* which were not identified at the species level, ascribed to the genera *Alternaria*, *Aspergillus*, *Beauveria*, *Epicoccum*, *Fusarium*, *Gelasinospora*, *Geotrichum*, *Phoma* and *Phomopsis* [280]. Evidence as taxane producers has been also reported for strains of *Cladosporium langeronii* and *Phomopsis* sp. from *Wollemia nobilis* [281].

## 10. Quinoline Alkaloids

Camptothecin (CPT) is probably the best known representative of this group, whose importance and history as a plant-derived antitumor drug to be widely found as a secondary metabolite of endophytic fungi seems to retrace what just described for taxol. In fact, in the last decade, this compound, and its analogues 9-methoxycamptothecin (MCPT) and 10-hydroxycamptothecin (HCPT) (Figure 9), have been reported from a number of endophytes from *Camptotheca acuminata* and a few more trees in the unrelated botanical family of the Icacinaceae (Table 4).

The attempt to obtain CPT by fermentation has evidenced a fundamental problem which may affect the possible use of endophytic fungal strains for production of bioactive plant metabolites on a large scale. In fact, the loss of the biosynthetic ability has been documented in a number of strains of

*F. solani* [282] and *Aspergillus* sp. [283]. This breakdown seems not to be related to the antibiotic properties of the compound, considering that resistance to CPT has been documented for a number of endophytic strains from *C. acuminata* [284], and it is intrinsic and not related to the biosynthetic aptitude [285]. On the other hand, production of camptothecins can be stimulated by exploiting the eliciting effects of a few organic and inorganic compounds, particularly salicylic acid which induced a higher HCPT yield by a strain of *Xylaria* sp. [286], and methyl jasmonate which increased CPT production by a strain of *T. atroviride* [283]. Furthermore, CPT production by a strain of *F. solani* from *C. acuminata* was notably increased by supplying an ethanolic extract of leaves of *C. roseus* containing strictosidine as a precursor in CPT biosynthesis, and even by ethanol itself [287].



**Figure 9.** Structures of quinoline alkaloids produced by endophytic fungi.

**Table 4.** Endophytic fungi producing camptothecin (CPT) and its analogues 9-methoxycamptothecin (MCPT) and 10-hydroxycamptothecin (HCPT).

Compounds	Fungal Species	Host Plants	References
CPT	<i>Entrophospora infrequens</i>	<i>Nothapodytes foetida</i>	[288,289]
CPT	<i>Neurospora</i> sp.	<i>N. foetida</i>	[290]
CPT	<i>Nodulisporium</i> sp.	<i>N. foetida</i>	[291]
CPT, HCPT, MCPT	<i>Fusarium solani</i>	<i>Camptotheca acuminata</i>	[292]
CPT, HCPT, MCPT	<i>F. solani</i>	<i>Apodytes dimidiata</i>	[293]
CPT	<i>Botryosphaeria parva</i>	<i>Nothapodytes nimmoniana</i>	[294]
CPT	<i>Diaporthe conorum</i>	<i>N. nimmoniana</i>	[294]
CPT	<i>Fusarium oxysporum</i>	<i>N. nimmoniana</i>	[294]
CPT	<i>Fusarium sacchari</i>	<i>N. nimmoniana</i>	[294]
CPT	<i>F. solani</i>	<i>N. nimmoniana</i>	[294]
CPT	<i>Fusarium</i> sp.	<i>N. nimmoniana</i>	[294]
CPT	<i>Fusarium subglutinans</i>	<i>N. nimmoniana</i>	[294]
CPT	<i>Fusarium verticillioides</i>	<i>N. nimmoniana</i>	[294]

Table 4. Cont.

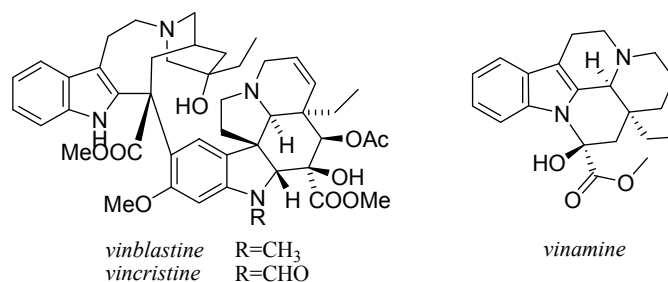
Compounds	Fungal Species	Host Plants	References
CPT	<i>Galactomyces</i> sp.	<i>N. nimmoniana</i>	[294]
CPT	<i>Irpex lacteus</i>	<i>N. nimmoniana</i>	[294]
CPT	<i>Phomopsis</i> sp.	<i>N. nimmoniana</i>	[294]
CPT	Unidentified strains	<i>N. nimmoniana</i>	[294]
HCPT	<i>Xylaria</i> sp.	<i>C. acuminata</i>	[286]
HCPT	<i>Valsa mali</i>	<i>C. acuminata</i>	[295]
CPT	<i>Aspergillus</i> spp.	<i>C. acuminata</i>	[283]
CPT	<i>Trichoderma atroviride</i>	<i>C. acuminata</i>	[283]
CPT, HCPT, MCPT	<i>Alternaria alternata</i>	<i>Miquelia dentata</i>	[296]
CPT, HCPT, MCPT	<i>Fomitopsis</i> sp.	<i>M. dentata</i>	[296]
CPT, HCPT, MCPT	<i>Phomopsis</i> sp.	<i>M. dentata</i>	[296]
CPT	<i>F. oxysporum</i>	<i>N. foetida</i>	[297]

A paramount pharmaceutical relevance also pertains to the cinchona-alkaloids (Figure 9) extracted from bark of quina trees (*Cinchona* sp.), representing fundamental drugs for malaria prophylaxis [298]. After reporting the first endophytic isolate (*Diaporthe* sp.) from *Cinchona ledgeriana* collected in Java (Indonesia) producing quinine, quinidine, cinchonidine, and cinchonine [299], additional 20 strains of *Phomopsis* sp., *Schizophyllum* sp., *Penicillium* sp., *Fomitopsis* sp., and *Arthrimum* sp. from the same source have been found to produce variable amounts of the these compounds [300,301].

Two more compounds in this class are to be considered in this review. Berberine (Figure 9) is a cardioprotective, antidiabetic, antibiotic and antitumor product known from several unrelated medicinal plants [302], which has been recently found as a secondary metabolite of a strain of *F. solani* from roots of the medicinal liana *Coscinium fenestratum* [303]. Sanguinarine (Figure 9), a benzyloisoquinoline or benzophenanthridine alkaloid known from several plants belonging to the Papaveraceae, whose antimicrobial effects have been particularly exploited for toothpastes and mouthwashes [304], has been found to be produced by a strain of *F. proliferatum* from leaves of *Macleaya cordata* [305].

## 11. Other Alkaloids

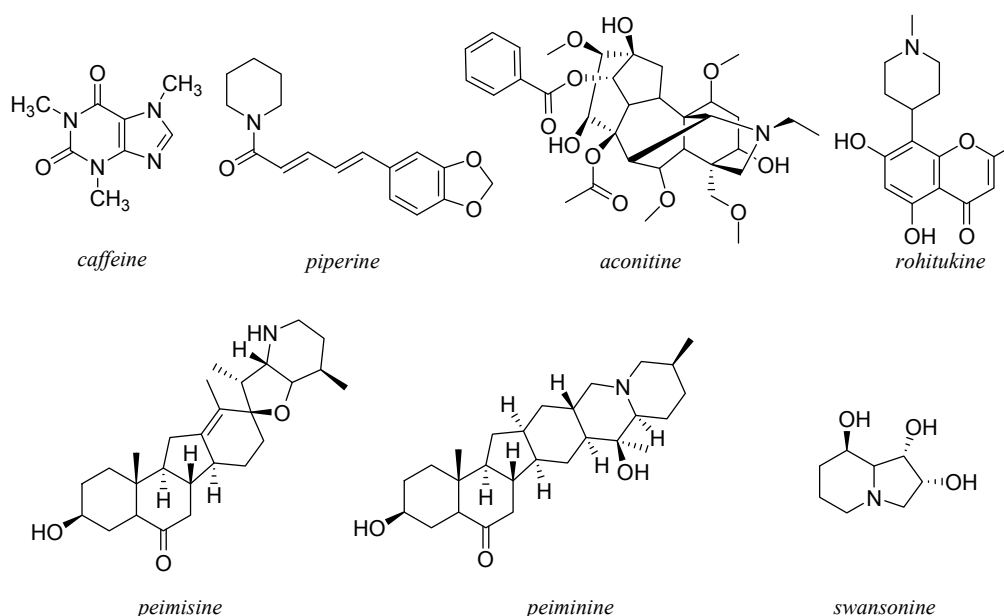
The vinca-alkaloids (Figure 10) are a series of over a hundred bioactive products extracted from periwinkle (*Catharanthus roseus*) and the related *Vinca* species, mostly exploited in cancer chemotherapy based on their action on tubulin and microtubule organization [306]. Endophytic strains of *Alternaria* sp. [307] and *F. oxysporum* [308] from *C. roseus* respectively produced vinblastine and vincristine, while more recently another strain of the latter species has been found to produce both compounds [309], and to synthesize vincristine from vinblastine when the latter compound was added to the growth medium [310]. Finally, an unidentified strain from *Vinca minor* has been reported for production of vincamine [311].



**Figure 10.** Structures of vinca-alkaloids.

Caffeine, the methylxanthine alkaloid (Figure 11) from *Coffea* spp. well known as a psychoactive drug, has been evidenced in extracts of unidentified endophytic fungi recovered from the Indian ethnomedicinal plants *Osbeckia chinensis*, *O. stellata* and *Potentilla fulgens* [43].

Piperine (Figure 11) is an alkaloid of *Piper longum* and *Piper nigrum* known for its antimycobacterial, antihyperlipidemic, anti-inflammatory, immunoregulatory and antitumor properties [312–314]. This valuable compound has been extracted from liquid cultures of endophytic strains of *Periconia* sp. from *P. longum* [315], and *Mycosphaerella* sp. [316] and *C. gloeosporioides* [317] from *P. nigrum*.



**Figure 11.** Structures of miscellaneous alkaloids produced by endophytic fungi.

Aconitine is a diterpenoid alkaloid (Figure 11) extracted as a secondary metabolite of *Aconitum* species, displaying analgesic, anti-inflammatory and antitumor activity. It has been also found as a fermentation product of an endophytic strain of *Cladosporium cladosporioides* recovered from roots of *Aconitum leucostomum* [318].

Rohitukine is a chromane alkaloid (Figure 11) with anti-inflammatory, immunomodulatory and antitumor properties first characterized as a secondary metabolite of a few tropical plants, *Amora rohituka* (= *Aphanamixis polystachya*) and *Dysoxylum binectariferum* (Meliaceae), *Schumanniphyton* (*Tetrastigma*) *magnificum* and *Schumanniphyton* (*Assidora*) *problematicum* (Rubiaceae) [319]. This compound has been recently reported as a fermentation product of endophytic

strains of *F. proliferatum*, *F. oxysporum* and *F. solani* from *D. binectariferum* [320,321], and *F. fujikuroi* from *A. rohituka* [321].

Peimisine and peiminine are steroidal alkaloids (Figure 11) known to occur in bulbs of *Fritillaria* spp. used as in Chinese ethnomedicine for their expectorant effects. A strain of an undetermined *Fusarium* species endophytic in bulbs of *Fritillaria unibracteata* var. *wabensis* has been found to produce these compounds [322].

Swainsonine is a trihydroxy inolidizine alkaloid (Figure 11) acting as a glycosidase inhibitor which occurs in a number of plant species, such as *Swainsona canescens*, *Ipomoea* spp., *Turbina cordata*, *Sida carpinifolia*, and locoweeds (*Astragalus* and *Oxytropis* spp.) [323]. The latter are forage plants whose consumption by livestock is associated to the syndrome of locoism. It has been observed that a fungal endophytic species occurring in locoweeds, the vertically-transmitted *Undifilum oxytropis* [324,325], previously described as *Embellisia* sp. [326,327], is capable to produce swainsonine *in vitro*. Novel species of *Undifilum*, *U. fulvum* and *U. cinereum*, have been later reported for production of this compound, respectively in *Astragalus lentiginosus* and *A. mollissimus* [328], along with strains of an unidentified *Undifilum* sp. recovered from *S. canescens* in Australia [329]. Moreover, the compound was found to be produced by endophytic isolates of *Fusarium tricinctum* recovered from *Oxytropis kansuensis* and *O. deflexa* in China [330]. The inhibitory properties on  $\alpha$ -mannosidase have been exploited for the development of swainsonine as an anticancer drug, which has been impaired by reason of undesirable side effects [331,332]. Finally, it is interesting to note that plants of *A. lentiginosus* and *Oxytropis sericea* germinated from the embryo, which is not colonized by endophytes, were found to be fungus free and did not contain swainsonine [333]. This evidence strongly supports the hypothesis that actually its occurrence in plants may entirely derive from biosynthesis by endophytic fungal strains.

## 12. 3-Nitropropionic Acid

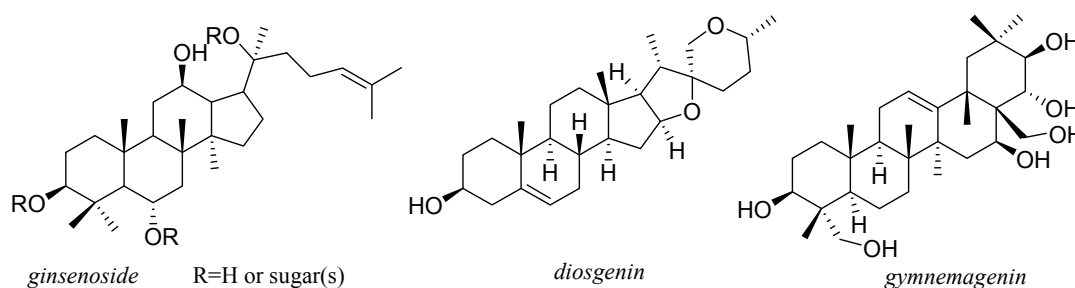
Analogous for its effects in livestock intoxication, 3-nitropropionic acid (NPA) is a secondary metabolite involved in the nitrification process in Leguminosae [334], particularly of the genera *Hippocrepis*, *Lotus*, *Scorpiurus* and *Securigera*, and the species *Astragalus falcatus* and *Coronilla viminalis* [335]. The fact that the latter are the only species in the respective genera to be reported to produce this compound has raised the interrogative if it is actually produced by associated endophytic microorganisms. In fact NPA is mainly known as a toxin from a number of fungal species [336–338], and mentioned as a product of endophytic fungi such as *Melanconium betulinum* from birches in Germany [339], and a number of *Phomopsis* species, including *P. phaseoli* (= *Diaporthe phaseolorum*) from an unidentified rainforest tree of Guyana [339], and *P. longicolla* from *Trichilia elegans* in Brazil [340]. Isolates of *Phomopsis* spp. from crêpe ginger (*Costus* sp.) in Costa Rica and from Thai medicinal plants also produce this compound, together with a few strains of unidentified species from the latter source [335,341].

## 13. Saponines

Saponines are glycosides where the sugar moiety is bound through a glycosidic linkage to an aglycone (sapogenin) which can be a triterpenoid or a steroid compound. Generally considered as

antinutritional factors, these products have been recently re-evaluated for their nutraceutical properties deriving from consistent anticholesterolemic effects and inhibition of sugar and ethanol absorption. Additional antibiotic, antitumor and immunomodulatory properties have also been reported [342]. Saponins are known to occur in many taxonomically unrelated plants, but there is an increasing evidence that their production is also widespread among endophytic fungi. Again such a biosynthetic ability may represent an aspect of the mutualistic relationships established in view of plant defense, considering that some plant pathogens are reported to have developed saponin-detoxifying enzymes as a virulence factor [343]. To this regard, production of saponins has been recently documented for strains of *Aspergillus* sp. from *Salvadora oleoides* [344] and *Justicia beddomei* [345], *Aspergillus* sp., *Bulgaria* sp. and *Sirococcus conigenus* from *Potentilla fulgens* [346], *A. niger* and *F. oxysporum* from *Crotalaria pallida* [347], *A. alternata*, *A. niger* and *Penicillium* sp. from *Loranthus* sp. [348], *A. alternata*, *A. flavus*, *A. niger*, *Colletotrichum gleosporioides* and *Trichoderma* sp. from *Tabebuia argentea* [197], *Cochliobolus lunatus* (anamorph *Curvularia lunata*) from *Boswellia ovalifoliolata*, and *Monochaetia karstenii* (= *Pestalotiopsis maculans*) and *Phyllosticta* sp. from *Shorea thumbuggaia* [349], *Aspergillus neoniveus* (= *Fennellia nivea*) from *Typhonium divaricatum* [350], *A. alternata*, *A. flavus*, *A. niger*, *Cladosporium* sp., *Penicillium* sp., *Phomopsis* sp. and *Trichoderma* sp. from *Aegle marmelos* [351], *A. niger*, *A. terreus*, *Aspergillus* sp., *Aspergillus tubingensis*, *Coprinopsis cinerea*, *C. lunata* and *Fusarium* sp. from *Eugenia jambolana* [352], *Aspergillus awamori* and again *C. gleosporioides* from *Rauwolfia serpentina* [353].

More particularly, the ginsenosides (Figure 12), previously characterized from plants in the genus *Panax*, have been extracted from cultures of root endophytic strains of *Penicillium* sp., *Dictyochaeta* sp. and *Camarosporium* sp. from *Aralia elata* [354], and of *Fusarium* sp., *Aspergillus* sp. and *Verticillium* sp. from *P. ginseng* [355]. However, the ability by endophytic strains of *F. oxysporum*, *Fusarium* sp. and *Nodulisporium* sp. from *Panax notoginseng* to transform ginsenosides to yield additional analog compounds [356] demonstrates that endophytic fungi directly contribute to the particular pattern of these compounds occurring in plant tissues.



**Figure 12.** Structures of saponines produced by endophytic fungi.

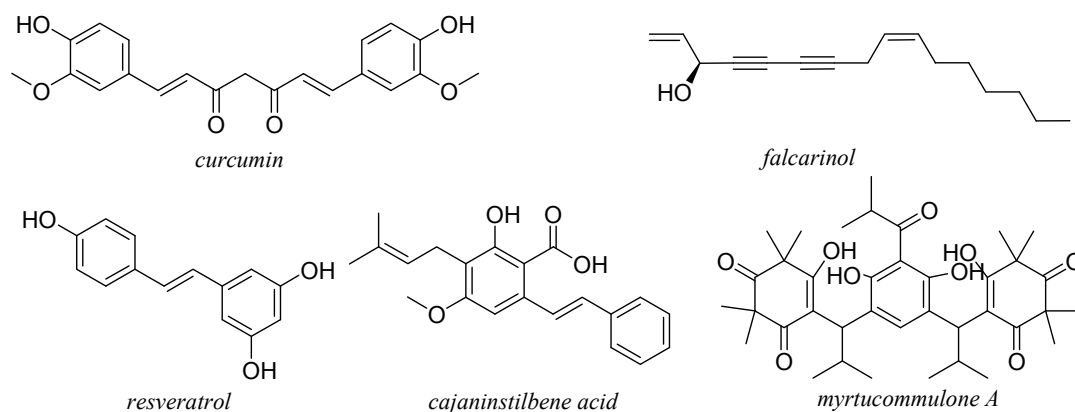
A similar effect has been documented for an endophytic strain of *Fusarium* sp. from *Dioscorea nipponica* which was able to increase diosgenin content in its liquid cultures added with a rhizome extract of the host plant [357]. Diosgenin is a steroidal sapogenin (Figure 12) known as a secondary metabolite of a number of plant species, particularly the yams (*Dioscorea* spp.). It is an important precursor for production of semi-synthetic steroids, such as corticosteroids, progesterone and other steroidal drugs, and displays a number of important pharmacological effects [358]. This valuable compound is also

produced by endophytic strains of *Cephalosporium* sp. and *Paecilomyces* sp. from *P. polyphylla* var. *yunnanensis* [359,360]. *In vitro* cell culturing represents an alternative means for production of this drug, considering that natural populations of one of the most important sources, the yellow ginger (*Dioscorea zingiberensis*), are decreasing due to overexploitation, and agricultural production is problematic by reason of the 3–4 years required for obtaining mature rhizomes. Oligosaccharides and polysaccharides extracted from an endophytic strain (Dzf17) of *F. oxysporium* have been found to elicit growth and diosgenin production in cell cultures of *D. zingiberensis* [361,362]. The same effect was also observed when both cell cultures and seedlings were treated with beauvericin produced by an endophytic strain of *Fusarium redolens* from the same plant species [363].

Gymnemagenin, a triterpenoid sapogenin (Figure 12) extracted from the renowned anti-diabetic herb *Gymnema sylvestre*, has been found as a fermentation product of an endophytic strain of *Penicillium oxalicum* recovered from leaves of this plant in India [364].

#### 14. Miscellaneous Compounds

Resveratrol (Figure 13) is a stilbene phytoalexin produced by many plants in response to biotic and abiotic injuries, and a reputed nutraceutical based on its antioxidant properties [365]. A number of endophytic strains from *Vitis vinifera*, *Vitis quinquangularis*, and *P. cuspidatum* belonging to the genera *Alternaria*, *Aspergillus*, *Botryosphaeria*, *Cephalosporium*, *Geotrichum*, *Mucor* and *Penicillium* were found to be able to produce this compound; however, only a *Alternaria* strain retained this capability after repeated culturing cycles [366]. Another leaf strain of *Alternaria*, together with root strains of *F. solani*, *F. oxysporum* and *F. proliferatum* from *C. cajan*, have been found to produce cajanin stilbene acid (Figure 13), a related antioxidant compound originally characterized from the host plant [367].



**Figure 13.** Structures of miscellaneous compounds produced by endophytic fungi.

Mainly used as a food additive, curcumin (Figure 13) is a diarylheptanoid compound of turmeric (*Curcuma longa*) with potential pharmaceutical applications [368], which has been recently found as a fermentation product of a previously-mentioned endophytic strain from *C. wenyujin* [39].

Faltarinol, also known as carotatoxin or panaxynol (Figure 13), is a fatty alcohol reported from several unrelated plant species such as carrots (*Daucus carota*) and other Apiaceae, red ginseng (*P. ginseng*), ivies (*Hedera* spp.) and other Araliaceae. It is considered a natural pesticide protecting

roots from fungal diseases, and displayed some extent of activity against certain types of cancer [369]. Production of this compound has been reported by a strain of *Paecilomyces* sp. from *P. ginseng* [104].

Myrtucommulones are acylphloroglucinol compounds extracted from myrtle (*Myrtus communis*) and related plants in the Myrtaceae considered as prospect pharmaceuticals based on consistent antibacterial, antimalarial, antioxidant, anti-inflammatory and antitumor properties. So far 13 analogues (myrtucommulones A-M) have been characterized from plant sources, and the production of myrtucommulone A (Figure 13) and D has been recently reported from a myrtle endophytic strain of *Neofusicoccum australe* (teleomorph *Botryosphaeria australis*) [370].

Finally, the widespread pentacyclic triterpenoid compound ursolic acid, also known as prunol or malol, and reported for its anticancer and cardioprotective properties [371], has been recently found in extracts of a cited endophytic strain of *A. stygium* [51].

## 15. Future Perspectives

Data considered in this review highlight a continuously increasing number of plant-derived bioactive products also occurring as secondary metabolites of endophytic fungal strains. Therefore, it is quite easy to foresee that the finding of additional such compounds is under way and may disclose further applicative opportunities. As an example, the reported production of colchatetralene, a structural analog of colchicine, by an endophytic strain (*Aspergillus* sp.) from seeds of *Gloriosa superba* [372] has paved the way for the possible production of this important drug by a microbial agent. Moreover, indications have been reported concerning the possible production of the secoiridoid glycoside gentiopicroin and of the cardiotonic drug digoxin by endophytic fungal strains, respectively from *Gentiana macrophylla* [373] and *Digitalis lanata* [374], and more circumstantiated studies are expected for these important compounds.

Within the above-considered categories, volatile compounds from essential oils particularly represent a mine to be dug more in depth. In fact benzophenone derivatives, which are biosynthetically related to xanthenes and known as main components of the scent of species in a few botanical families such as Clusiaceae, Gentianaceae, Moraceae, Polygalaceae, Rosaceae and Thymelaceae, are also widespread secondary metabolites of fungi [375]. Therefore, it would not be surprising if additional compounds previously reported from plants are also evidenced as fermentation products of endophytic strains [376–378].

The likely finding by endophytic strains has been also anticipated for asperphenamate, a phenylalanine derivative recently attracting attention for its antitumor properties. In fact this compound was first characterized from *Aspergillus flavipes* and a number of fungi which are also known for their endophytic habit. Therefore, its subsequently observed occurrence in many botanically unrelated plant species is considered to possibly derive by the biosynthetic ability of endophytic fungal strains [379]. Besides the above-mentioned case of swainsonine, a more direct proof that some plant metabolites can be actually produced by their associated endophytic fungi has been provided by the finding of the mycotoxin alternariol, along with the related compounds altenusin and alternariol 5-*O*-methyl ether, in foliar extracts of the medicinal plant *Polygonum senegalense* harboring an *Alternaria* strain [380]. The latter compound had been also extracted from *Anthocleista djalensis*, a tree used in traditional medicine in West Africa [381].

Further investigational opportunities arise from the ability by endophytic fungi to modify plant metabolites into novel bioactive compounds, and actually several examples of such a kind of biochemical interaction have been reported so far. A strain of *Xylaria* sp. associated with *Cinchona pubescens* was found to be able to convert the above-mentioned *Cinchona* alkaloids into their 1-*N*-oxides [382]. Strains of *Diaporthe* spp. from the tea plant (*Camellia sinensis*) and from rhizome of *C. longa* respectively performed the stereoselective oxidation of (+)-catechin and (–)-epicatechin into the corresponding 3,4-*cis*-dihydroflavan derivatives [383,384], and the conversion of curcumin into a few colorless hydroderivatives [385]. Moreover, an unidentified strain from yellow moonshed (*Archangelisia flava*) has been reported to convert berberine into its 7-*N*-oxide derivative [386].

On the other end, endophytic fungi may also have a role in degradation of plant metabolites. As an example, a strain of *Phomopsis liquidambari* from the stem of Chinese bishopwood (*Bischofia polycarpa*) has been showed to degrade the phytoestrogen luteolin and additional phenolic compounds such as phenanthrene [387], introducing the possible employment of endophytic fungal strains in bioremediation [388].

However, there is no doubt that in the future the most intriguing research hint concerns the genetic bases of production of bioactive metabolites by these closely associated but phylogenetically unrelated organisms. Although a negationist point of view has been advanced concerning taxol biosynthesis by endophytes [389], taken as a whole the over 300 cases mentioned in this review concerning homologous and heterologous endophytic strains producing plant bioactive compounds represent a compelling evidence that these micorganisms and their host plants interact at some level in the biosynthetic process. The main hypothesis is that these interactions may lead to horizontal gene transfers or genetic recombinations, from the plant to its endophytic counterpart and/or *vice-versa*, originating novel specialized strains able to accumulate certain metabolites in the host tissues [186], which would be a good reason to explain why in the end a mutualistic relationship is established. The fact that most of these compounds have been originally extracted from plants has generated a somehow misleading preconception that it is the endophytic microbe that for some reasons acquires the ability to produce a given plant metabolite. However, actually, the finding of taxol and other bioactive products from endophytic strains of plants which themselves are not reported as a source of the same compound could be considered as an indication that a reverse influence may be more likely. On the other hand, investigations concerning complex diterpenoid compounds, such as gibberellins and again taxol, have shown that the biosynthetic pathways in plant and endophytes may differ at some level [5,251], which is a clue for an independent development of the subtended genetic traits. However, in the end, the problem is again preconceptual, since it cannot be excluded that such a variation in the biosynthetic scheme may also exist within the categories of both plants and associated endophytes.

An even more complex situation could result if further evidence is provided that synthesis of bioactive metabolites in fungi is in turn influenced by other associated microbes. This is the case of rhizoxin which has been found to be actually synthesized by an endosymbiotic bacterium (*Burkholderia rhizoxinica*) residing in the cytosol of the rice fungal pathogen *Rhizopus microsporus* [390,391]. Moreover, such a kind of provision may well occur in endophytic fungi, considering that a widespread presence of endohyphal bacteria resulted in a survey on Ascomycetous endophytes of Cupressaceae [392]. Moreover, a role of giant linear plasmids in the synthesis of antibiotic compounds in *Streptomyces* has been proposed since over 25 years [393]. If eventually confirmed for other metabolites, the role of

these “third parties” could represent the means through which the biosynthetic abilities are interchanged between plants and their associated endophytes, and also explain why in a few cases this property is lost after repeated subculturing. This latter undesired aspect, which is reported to impair an efficient employment of endophytic fungi by the pharmaceutical industry, might also be consequential to more subtle events at the gene level, considering that the plant-endophyte interaction may involve promotion of gene transcriptions. Coherent with this possibility are the eliciting properties observed by endophytes on the synthesis of a number of bioactive plant products, with a few cases previously mentioned in this review [193,361,362]. Finally, an intriguing eliciting function may also characterize other cohabiting endophytic strains not directly capable to produce a given metabolite, as shown in the case of strains of *Alternaria* sp. and *Phomopsis* sp. which consistently increased taxol synthesis by a taxol-producer *Paraconiothyrium* sp. from *Taxus x media* in co-cultures [394].

Quite clearly, the complex evolving scenario outlined in this paper is introductory to further advances in the elucidation of the genetic and biochemical bases of the synthesis of bioactive compounds, and the reflecting biocenotic interactions among plants, their associated endophytes and other involved microorganisms. New acquisitions in these fields will be fundamental in order to exploit microbial strains for a large-scale production of plant-derived drugs in controlled fermentative processes.

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## Author Contributions

Authors contributed equally to this review.

## Conflicts of Interest

The authors declare no conflict of interest.

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