



Review

Fungal Endophytes as Efficient Sources of Plant-Derived Bioactive Compounds and Their Prospective Applications in Natural Product Drug Discovery: Insights, Avenues, and Challenges

Archana Singh ^{1,2}, Dheeraj K. Singh ^{3,*} , Ravindra N. Kharwar ^{2,*} , James F. White ^{4,*} and Surendra K. Gond ^{1,*}¹ Department of Botany, MMV, Banaras Hindu University, Varanasi 221005, India; singh.archi90@gmail.com² Department of Botany, Institute of Science, Banaras Hindu University, Varanasi 221005, India³ Department of Botany, Harish Chandra Post Graduate College, Varanasi 221001, India⁴ Department of Plant Biology, Rutgers University, New Brunswick, NJ 08901, USA

* Correspondence: dheeru.bhu@gmail.com (D.K.S.); rnkharwar@gmail.com (R.N.K.); jwhite3728@gmail.com (J.F.W.); surendragond@gmail.com (S.K.G.)

Abstract: Fungal endophytes are well-established sources of biologically active natural compounds with many producing pharmacologically valuable specific plant-derived products. This review details typical plant-derived medicinal compounds of several classes, including alkaloids, coumarins, flavonoids, glycosides, lignans, phenylpropanoids, quinones, saponins, terpenoids, and xanthenes that are produced by endophytic fungi. This review covers the studies carried out since the first report of taxol biosynthesis by endophytic *Taxomyces andreanae* in 1993 up to mid-2020. The article also highlights the prospects of endophyte-dependent biosynthesis of such plant-derived pharmacologically active compounds and the bottlenecks in the commercialization of this novel approach in the area of drug discovery. After recent updates in the field of ‘omics’ and ‘one strain many compounds’ (OSMAC) approach, fungal endophytes have emerged as strong unconventional source of such prized products.

Keywords: endophytic fungi; medicinal plants; plant-derived; host-derived; bioactive; natural products; secondary metabolites; drug discovery



Citation: Singh, A.; Singh, D.K.; Kharwar, R.N.; White, J.F.; Gond, S.K. Fungal Endophytes as Efficient Sources of Plant-Derived Bioactive Compounds and Their Prospective Applications in Natural Product Drug Discovery: Insights, Avenues, and Challenges. *Microorganisms* **2021**, *9*, 197. <https://doi.org/10.3390/microorganisms9010197>

Received: 17 November 2020

Accepted: 13 January 2021

Published: 19 January 2021

Publisher's Note: MDPI stays neutral with regard to jurisdictional claims in published maps and institutional affiliations.



Copyright: © 2021 by the authors. Licensee MDPI, Basel, Switzerland. This article is an open access article distributed under the terms and conditions of the Creative Commons Attribution (CC BY) license (<https://creativecommons.org/licenses/by/4.0/>).

1. Introduction

Several recent reports suggest that natural products may play a substantial role in the drug discovery and development process as a source of diverse and novel templates for future drugs [1–4]. With the rapidly evolving recognition that significant numbers of natural products are either produced by microbes or a result of microbial interactions with their hosts, the area of endophyte research for natural products is positioned to take the drug discovery and development process to the next level [5,6]. In the backdrop of the past 25 years of studies, endophytes may be defined as a polyphyletic group of unique microorganisms residing in healthy living internal tissues of the plants with covert and/or overt positive effects on their hosts. They establish a variety of intricate biological intra- and inter-relationships among them and with their hosts, respectively. Endophytes are able to produce a multitude of secondary metabolites with diverse biological activities [7–9]. However, merely 0.75–1.50% of known plant species has been explored for their endophytes yet. So, the opportunity to find new potential bioactive metabolites from cryptic endophytic microorganisms of nearly 374,000–400,000 plant species congruently occupying millions of biological niches is considered high [5,10]. This opportunity has increased further with the innovative discovery of biosynthesis of *Taxus* derived anticancer compound ‘taxol’ from its endophytic fungus *T. andreanae* in 1993 by Stierle et al. [11]. This discovery leads to renewed attention in endophytic fungi for isolating plant-derived

medicinal compounds [12–14]. Later, a series of works revealed that a reasonable number of plant-derived compounds are synthesized by endophytes rather than hosts [9,15]. However, there are unsettled and contradictory reports regarding the phylogenetic origin of genes related to the biosynthesis pathway of such plant-derived compounds in host plants and their microbial endophytes [16]. The above facts prompted us to use the word “plant/host-derived” rather than “plant/host-origin” for such compounds. Nevertheless, it is now an established fact that endophytes can co-/produce, induce, and/or modify a plethora of “specific plant-derived” metabolites in-/outside of host plants [12,14,17]. Such discoveries opened the new horizons for the up-scaled production of plant-derived medicinal compounds from endophytes. The recent increase in demand for natural products and difficulties in accessing them from plants make endophytes interesting targets for the assessment and isolation of typical host-derived compounds [18,19]. Since medicinal plants are an inherent source of many therapeutic compounds, it is vital to explore their endophytes to isolate such compounds. The current review aims to provide an up-to-date overview on the globally isolated specific plant-derived bioactive compounds synthesized by fungal endophytes from the period 1993 to mid-2020. It will also focus on applications and modes of actions of such compounds. This review will also provide insights about different challenges in employing endophytes as an alternative source for the synthesis of plant-derived bioactive compounds and their application in drug discovery. Its outcome would certainly lead to strategize the use of endophytes as an efficient novel source for plant-derived metabolites.

2. Plant-Derived Bioactive Natural Products from Fungal Endophytes

A wide array of secondary metabolites in fungi is biosynthesized from very few key precursor compounds by slight variations in basic biosynthetic pathways and can be classified into nonribosomal peptides, polyketides, terpenes, and alkaloids. Nonribosomal peptides are biosynthesized by multimodular nonribosomal peptide synthetases (NRPS) enzymes using both proteinogenic and nonproteinogenic amino acids. Polyketides are biosynthesized by polyketide synthase (PKS) enzymes from acetyl-CoA and malonyl-CoA units. Terpenes consisting of isoprene subunits are biosynthesized from the mevalonate pathway catalyzed by terpene cyclase enzymes. Alkaloids are nitrogen-containing organic compounds biosynthesized as complex mixtures through the shikimic acid and the mevalonate pathways, as they are usually derived from aromatic amino acids and dimethylallyl pyrophosphate [20]. Other classes of fungal secondary metabolites are linked with the above four groups of compounds. For ease and better understanding, we have classified different fungal secondary metabolites as alkaloids, coumarins, flavonoids, lignans, saponins, terpenes, quinones, and xanthenes, and miscellaneous compounds. Coumarins are a class of lactones consisting of a benzene ring fused to a α -pyrone ring and are mainly biosynthesized by the shikimic acid pathway from cinnamic acid. Flavonoids are synthesized by the phenylpropanoid pathway from phenylalanine using enzymes phenylalanine ammonia lyase (PAL), chalcone synthase, chalcone isomerase, and flavonol reductase [21]. Lignans are low molecular weight polyphenols biosynthesized by enzymes pinoresinol-lariciresinol reductase (PLR), PAL, cinnamoyl-CoA reductase (CCR), and cinnamyl-alcohol dehydrogenase (CAD) [22]. Saponins are glycosides containing a non-sugar triterpene or steroid aglycone (sapogenin) attached to the sugar moiety. Saponins are derived from intermediates of the phytosterol pathway using enzymes oxidosqualene cyclases (OSCs), cytochromes P450 (P450s), and UDP-glycosyltransferases (UGTs) [23]. Quinones are biosynthesized through several pathways; for example, isoprenoid quinones are synthesized by the shikimate pathway using chorismite-derived compounds as precursors, terrequinone by NRPS from L-tryptophan, dopaquinone by tyrosinase from tyrosine, and benzoquinone by catechol oxidase/PKS from catechol [24]. Xanthenes comprise an important class of oxygenated heterocyclics biosynthesized through the polyacetate/polymalonate pathway by the internal cyclization of a single folded polyketide chain [25].

2.1. Plant-Derived Alkaloids from Fungal Endophytes

After a systematic literature survey, we enlisted 19 plant-derived medicinal alkaloids that have been produced by different endophytic fungi (Table 1), and some important alkaloids are described below.

Table 1. Plant-derived alkaloids produced by endophytic fungi.

Plant-Derived Alkaloids	Activities/Applications	Plant Source	Endophytic Source	Host Plant	References
Aconitine	Anticancer, anti-inflammatory, anti-neuralgic, cardiotoxic	<i>Aconitum</i> spp.	<i>Cladosporium cladosporioides</i>	<i>Aconitum leucostomum</i>	[26]
Berberine	Antibiotic, antidiabetic, antihypertensive, antiproliferative hepatoprotective, hypolipidemic, vasodilator	<i>Berberis</i> spp., <i>Cosciniium fenestratum</i> , <i>Hydrastis canadensis</i> , <i>Phellodendron amurense</i>	<i>Alternaria</i> sp.	<i>Phellodendron amurense</i>	[27]
			<i>Fusarium solani</i>	<i>Cosciniium fenestratum</i>	[28,29]
Caffeine	CNS stimulant	<i>Coffea</i> spp., <i>Theobroma cacao</i>	Anonymous endophytes	<i>Osbeckia chinensis</i> , <i>Osbeckia stellata</i> , <i>Potentilla fulgens</i>	[30]
			<i>Entrophospora infrequens</i>	<i>Nothapodytes foetida</i>	[31]
			<i>Entrophospora infrequens</i>	<i>Nothapodytes foetida</i>	[32]
			<i>Neurospora</i> sp.	<i>Nothapodytes foetida</i>	[33]
			<i>Valsa mali</i>	<i>Camptotheca acuminata</i>	[34]
			<i>Nodulisporium</i> sp.	<i>Nothapodytes foetida</i>	[35]
			<i>Fusarium solani</i>	<i>Camptotheca acuminata</i>	[36]
Camptothecin	Antitumor	<i>Camptotheca acuminata</i> , <i>Miquelia dentata</i> , <i>Nothapodytes nimmoniana</i> , <i>Ophiorrhiza</i> spp.	<i>Botryosphaeria parva</i> , <i>Diaporthe conorum</i> , <i>Fusarium oxysporum</i> , <i>Fusarium sacchari</i> , <i>Fusarium solani</i> , <i>Fusarium subglutinans</i> , <i>Fusarium verticillioides</i> , <i>Galactomyces</i> sp., <i>Irpex lacteus</i> , <i>Phomopsis</i> sp., <i>Fusarium</i> sp.	<i>Nothapodytes nimmoniana</i>	[37]
			<i>Xylaria</i> sp.	<i>Camptotheca acuminata</i>	[38]
			<i>Fusarium solani</i>	<i>Apodytes dimidiata</i>	[39]

Table 1. Cont.

Plant-Derived Alkaloids	Activities/Applications	Plant Source	Endophytic Source	Host Plant	References
			<i>Botryosphaeria dothidea</i>	<i>Camptotheca acuminata</i>	[40]
			<i>Alternaria alternata</i> , <i>Fomitopsis</i> sp., <i>Phomopsis</i> sp.	<i>Miquelia dentata</i>	[41]
			<i>Trichoderma atroviride</i>	<i>Camptotheca acuminata</i>	[42]
			<i>Aspergillus</i> sp.	<i>Camptotheca acuminata</i>	[36]
			<i>Fusarium oxysporum</i>	<i>Nothapodytes foetida</i>	[43]
Capsaicin	Anti-inflammatory, gastro-stimulatory	<i>Capsicum annuum</i>	<i>Alternaria alternata</i>	<i>Capsicum annuum</i>	[44]
Homoharringtonine	Anticancer	<i>Cephalotaxus</i> spp.	<i>Alternaria tenuissima</i>	<i>Cephalotaxus</i> sp.	[45]
			<i>Acremonium</i> sp.	<i>Huperzia serrata</i> (syn. <i>Lycopodium serratum</i>)	[46]
			<i>Blastomyces</i> sp., <i>Botrytis</i> sp.	<i>Phlegmariurus cryptomerianus</i>	[47]
			<i>Penicillium chrysogenum</i>	<i>Huperzia serrata</i>	[48]
			<i>Shiraia</i> sp.	<i>Huperzia serrata</i>	[49]
			<i>Cladosporium cladosporioides</i>	<i>Huperzia serrata</i>	[50]
Huperzine A	Acetylcholinesterase inhibitor, Alzheimer's treatment	<i>Huperzia serrata</i>	<i>Colletotrichum</i> sp., <i>Trichoderma</i> sp.	<i>Huperzia serrata</i>	[51]
			<i>Paecilomyces tenuis</i>	<i>Huperzia serrata</i>	[52]
			<i>Aspergillus flavus</i> , <i>Mycocleptodiscus terrestris</i> , <i>Penicillium griseofulvum</i>	<i>Huperzia serrata</i>	[53]
			<i>Penicillium</i> sp.	<i>Huperzia serrata</i>	[54]
			<i>Fusarium</i> sp.	<i>Phlegmariurus taxifolius</i>	[55]
			<i>Fusarium</i> sp.	<i>Huperzia serrata</i>	[56]
Peimisine, Imperialine-3b-D-glucoside	Antiasthmatic, antitumor, expectorant	<i>Fritillaria</i> spp.	<i>Fusarium</i> sp.	<i>Fritillaria unibracteata</i> var. <i>wabuensis</i>	[57,58]
			<i>Fusarium redolens</i>	<i>Fritillaria unibracteata</i> var. <i>wabuensis</i>	[59]

Table 1. Cont.

Plant-Derived Alkaloids	Activities/Applications	Plant Source	Endophytic Source	Host Plant	References
Piperine	Anti-inflammatory, anticancer, antimicrobial, antidepressant, hepatoprotective	<i>Piper longum</i> , <i>Piper nigrum</i>	<i>Periconia</i> sp.	<i>Piper longum</i>	[60]
			<i>Colletotrichum gloeosporioides</i>	<i>Piper nigrum</i>	[61]
			<i>Mycosphaerella</i> sp.	<i>Piper nigrum</i>	[62]
			<i>Phomopsis</i> sp.	<i>Oryza sativa</i>	[63]
Cinchona alkaloids: Quinine, Quinidine, Cinchonidine, Cinchonine	Antimalarial, antiarrhythmic, analgesic	<i>Cinchona</i> spp.	<i>Arthrinium</i> , <i>Fomitopsis</i> , <i>Diaporthe</i> , <i>Penicillium</i> , <i>Phomopsis</i> , <i>Schizophyllum</i>	<i>Cinchona ledgeriana</i>	[64]
			<i>Fusarium incarnatum</i> , <i>Fusarium oxysporum</i> (only quinine and cinchonidine) <i>Fusarium solani</i> (only quinine)	<i>Cinchona calisaya</i>	[65]
Rohitukine	Anticancer, CDK inhibitor, cytotoxic	<i>Amoora rohituka</i> <i>Dysoxylum binectariferum</i> ,	<i>Fusarium proliferatum</i>	<i>Dysoxylum binectariferum</i>	[66]
			<i>Fusarium oxysporum</i> , <i>Fusarium solani</i>	<i>Dysoxylum binectariferum</i>	[67]
			<i>Gibberella fujikuroi</i>	<i>Amoora rohituka</i>	[67]
Sanguinarine	Anticancer, antimicrobial, anti-inflammatory antioxidant, antihelminthic, neuroprotective	<i>Macleaya cordata</i> , <i>Sanguinaria canadensis</i>	<i>Fusarium proliferatum</i>	<i>Macleaya cordata</i>	[28,68]
Sipeimine	Antibechic, anti-ulcer	<i>Fritillaria</i> spp.	<i>Cephalosporium corda</i>	<i>Fritillaria ussuriensis</i>	[69]
Solamargine	Anticancer, cytotoxic	<i>Solanum nigrum</i>	<i>Aspergillus flavus</i>	<i>Solanum nigrum</i>	[70]
Swainsonine	Toxicosis in livestock	<i>Astragalus</i> , <i>Oxytropis</i> spp., <i>Swainsona canescens</i>	<i>Embellisia</i> sp.	<i>Astragalus</i> , <i>Oxytropis</i> spp.	[15,71]
			<i>Undifilum cinereum</i> , <i>U. fulvum</i>	<i>Astragalus lentiginosus</i> , <i>Astragalus mollissimus</i>	[72]
			<i>Fusarium tricinctum</i>	<i>Oxytropis deflexa</i> , <i>Oxytropis kansuensis</i>	[73]
			<i>Undifilum</i> sp.	<i>Swainsona canescens</i>	[74]

Table 1. Cont.

Plant-Derived Alkaloids	Activities/Applications	Plant Source	Endophytic Source	Host Plant	References
Vinblastine, Vincristine	Antitumor	<i>Catharanthus roseus</i> (syn. <i>Vinca rosea</i>)	<i>Alternaria</i> sp.	<i>Catharanthus roseus</i>	[75]
			<i>Fusarium oxysporum</i>	<i>Catharanthus roseus</i>	[76]
			<i>Fusarium oxysporum</i>	<i>Catharanthus roseus</i>	[77]
			<i>Talaromyces radicus</i>	<i>Catharanthus roseus</i>	[78]
			<i>Eutypella</i> spp.	<i>Catharanthus roseus</i>	[79]
			<i>Geomyces</i> sp.	<i>Nerium indicum</i>	[80]
Vincamine	Antihypertensive, vasodilator	<i>Vinca minor</i>	Anonymous	<i>Vinca minor</i>	[81]

2.1.1. Aconitine

Aconitine, a diterpenoid alkaloid found in *Aconitum* spp., is a voltage-gated sodium channel activator that effectively opens the Na⁺ channels causing the prolonged presynaptic depolarization of muscles and neurons. In Chinese folk medicine, aconitine is used for pain relief caused by trigeminal and intercostal neuralgia, rheumatism, migraine, and general debilitation. Aconitine is a strong cardiotoxic and neurotoxic agent, and its side effects may cause bradycardia, hypotension, ventricular dysrhythmia, and inhibition of the release of neurotransmitters [82]. Aconitine is also synthesized by endophytic fungus *Cladosporium cladosporioides* from *Aconitum leucostomum* [26].

2.1.2. Berberine

Berberine, an isoquinoline alkaloid found in *Berberis* spp. and some other plants (Table 1), is widely used in the treatment of hyperglycemia, hyperlipidemia, gastrointestinal, cardiovascular, renal, and neural disorders. The antidiabetic efficacy of berberine is comparable to that of the popular drug metformin. Its hypoglycemic effect is exerted via inhibition of mitochondrial function, stimulation of glycolysis, activation of AMP-activated protein kinase (AMPK)/AMPK pathway, and increasing insulin sensitivity. Moreover, berberine has additional advantageous effects on diabetic cardiovascular complications due to its antihypercholesterolemic, anti-arrhythmias, and nitric oxide (NO)-inducing properties. The antioxidant and aldose reductase inhibitory activities of berberine is useful in alleviating diabetic nephropathy [83]. Berberine specifically binds with DNA to inhibit replication, which confers its cytotoxicity and anticancer properties [28]. Moreover, the low toxicity of berberine makes it a potent future antidiabetic and antiproliferative agent. Berberine production has also been reported from endophytic fungi *Alternaria* sp. and *Fusarium solani* isolated from *Phellodendron amurense* and *Cosciniium fenestratum*, respectively [27,29].

2.1.3. Camptothecin

Camptothecin (CPT), a potent anticancer quinoline indole alkaloid, was first isolated from the bark of the *Camptotheca acuminata* in 1966, but it was also produced by some other plant species, including *Miquelia dentata*, *Nothapodytes nimmoniana*, and *Ophiorrhiza* [84]. Inadequate water solubility and high toxicity are two limiting factors for the application of CPT as an anticancer agent. However, its two derivatives 10-hydroxycamptothecin (HCPT), and 9-methoxycamptothecin (MCPT) retain the same medicinal efficacy without

above limitations [36]. CPT and HCPT reversibly stabilize the Top1–dsDNA complex by selectively inhibiting eukaryotic topoisomerase I (TopI) activity. In virtue of this, CPT derivatives are currently being used extensively as precursor compounds for efficient broad-spectrum anticancer drugs irinotecan, topotecan, and belotecan [36,85]. Recently, a chemically bespoke camptothecin–antibody drug conjugate named traztuzumabderuxtecán (Enhertu[®]) has also been approved by the US Food and Drug Administration (FDA) [9]. Puri et al. in 2005 and Rehman et al. in 2008 isolated the camptothecin-producing potential endophytic fungi *Entrophospora infrequens* and *Neurospora* sp. respectively from the inner bark of *Nothapodytes foetida* [31,33]. Again, endophytic fungus *F. solani* isolated from *C. acuminata* was found to produce CPT, HCPT, and MCPT [36]. Endophytic fungus *F. solani* isolated from *Apodytes dimidiata* in the Western Ghats, India also yielded camptothecin [39]. Three fungal species, *Alternaria alternata*, *Fomitopsis* sp., and *Phomopsis* sp., isolated from fruits of *M. dentata*, were found as prominent CPT producers [41]. In another bioprospection study, 161 fungal endophytes from *C. acuminata* were screened for CPT production in which *Botryosphaeria dothidea* was found as a prominent producer of MCPT [40]. Two camptothecin-producing fungi, *Trichoderma atroviride* and *Aspergillus* sp., were also isolated from *C. acuminata* [42,85]. CPT-producing endophytic fungi have also been isolated from *N. nimmoniana* [37,86]. We found a total of 22 CPT-producing endophytic fungal species from five different host plant species, as listed in Table 1. These findings suggested that the endophytic fungi could be a future alternative source of not only CPT but also of its safer and more efficient analogues.

2.1.4. Capsaicin

Capsaicin, a spicy alkaloid of red pepper *Capsicum annuum* first crystallized in 1878, has antilithogenic, anti-inflammatory, thermogenic, gastro-stimulatory, antidiabetic, cardio-protective, and anticancer attributes [87]. Capsaicin selectively binds to calcium channel protein targeting transient receptor potential vanilloid 1 (TRPV1) expressed by nociceptors and lowers its opening threshold, resulting in nociceptor depolarization. That is why capsaicin is linked to the sensation of heat and pain as well as obesity regulation via increased thermogenesis. Capsaicin decreases glucose tolerance by inhibiting adipose tissue inflammatory responses via decreasing adipose tissue macrophages and levels of inflammatory adipocytokines like tumor necrosis factor alpha (TNF- α), monocyte chemoattractant protein (MCP)-1, interleukin (IL)-6, and leptin. It also induces the TRPV1-dependent secretion of insulin and antihyperglycemic hormone glucagon. The potential beneficial effects of capsaicin on cardiovascular and gastroprotective systems are exhibited through the TRPV1-mediated release of neurotransmitter calcitonin gene related peptide (CGRP). Capsaicin exerts its anticancer activity via the activation of cAMP-activated protein kinase, peroxisome proliferator-activated receptor gamma (PPAR γ)-induced apoptosis, down-regulation of signal transducer and activator of transcription 3 (STAT3) target gene B-cell lymphoma 2 (Bcl-2), cell-cycle arrest by inhibiting cyclin-dependent kinases (CDK2, CDK4 and CDK6), modulation of the human epithelial growth factor receptor 2 (HER2) pathway and p27 expression, down-regulation of p38mitogen-activated protein kinase (MAPK), protein kinase B (PKB or AKT), and focal adhesion kinase (FAK) activation, and degradation of hypoxia inducible factor 1 α [88]. An endophytic fungal strain *A. alternata* isolated from fruits of *C. annuum* has also been found to produce capsaicin [44].

2.1.5. Homoharringtonine (HHT)

Valuable anticancer alkaloid homoharringtonine (HHT) for the first time has been isolated from the bark and leaves of threatened medicinal tree *Cephalotaxus harringtonia* [89]. It acts as a translation inhibitor during G₁ and G₂ phases of cell division. In 2012, homoharringtonine was approved for the treatment of chronic myeloid leukemia under generic name omacetaxine mepeosuccinate by the Food and Drug Administration of the USA [90]. Hu et al. in 2016 screened 213 fungal strains isolated from the bark of *Cephalotaxus haina-*

nensis for the HHT biosynthesis ability and found that *Alternaria tenuissima* was a stable HHT-producing endophyte [45].

2.1.6. Huperzine A

A tropical medicinal moss *Huperzia serrata* is clinically used for the treatment of Alzheimer's disease [54]. Its biologically active alkaloid huperzine A (HupA) acts as a strong acetylcholinesterase inhibitor (AChEI), which is a class of medication that improves the level of neurotransmitters in the brain and is hoped to be a potential treatment for Alzheimer's disease. Li et al. in 2007 first isolated an HupA-producing endophytic fungus *Acremonium* from *H. serrata* [46]. For now, 12 different HupA-producing endophytic fungal species from *H. serrata* and three from *Phlegmariurus* spp. have been reported by different workers (Table 1). Interestingly, many endophytic fungi have been shown to synthesize novel AChEIs in their metabolite extracts [91].

2.1.7. Peimisine and Imperialine-3 β -D-glucoside

Fritillaria, a traditional medicinal plant, is among the most widely used antitussive and expectorant drugs. The principal bioactive constituents of *Bulbus Fritillaria cirrhosa* are steroidal alkaloids peimisine and imperialine-3 β -D-glucoside [57]. *Fusarium* spp. isolated from *Fritillaria unibracteata* var. *wabensis* have also produced peimisine and imperialine-3 β -D-glucoside [58,59].

2.1.8. Piperine

Anti-inflammatory and anticancer alkaloid piperine is found in the fruits of *Piper longum* and *Piper nigrum* and responsible for their pungent taste. Piperine enhances hepatic-oxidized glutathione and decreases renal glutathione concentration and renal glutathione reductase activity, showing its antidiabetic activity. Piperine decreases liver marker enzymes activity, inhibits lipopolysaccharide-induced expression of interferon regulatory factor, reduces the activation of STAT1, and inhibits the release of Th-2-mediated cytokines indicating its anti-inflammatory activity. Piperine expresses its anticancer activity through the following mechanisms: activates caspase-3 and caspase-9, cleaves poly(ADP-ribose) polymerase (PARP), decreases Bcl-2 protein expression and increases Bax protein, reduces the expression of phosphorylated STAT3 and nuclear factor kappa B (NF- κ B) transcription factors, blocks extracellular signal-regulated kinase (ERK1/2), p38 MAPK, and AKT signaling pathways, and suppresses epidermal growth factor (EGF)-induced matrix metalloproteinase (MMP)-9 expression [92]. It has bioavailability-enhancing ability for certain drugs and nutrients. It has also been extracted from the cultures of endophytic fungi *Periconia* sp., *C. gloeosporioides*, and *Mycosphaerella* sp. isolated from *Piper* spp. [60–62]. Recently, piperine production has also been reported from endophytic *Phomopsis* sp. from *Oryza sativa* [63].

2.1.9. Quinine

The stem bark and roots of the *Cinchona* spp. are well-established sources of quinine. It has been used as the only effective medication for malaria for centuries until the development of synthetic antimalarial drugs in 1940s. Quinine functions as an antimalarial by acting as an intra-erythrocytic schizonticide and also as gametocytocidal for *Plasmodium malariae* and *Plasmodium vivax* but not for *Plasmodium falciparum* [93]. One of the earliest reports regarding the endophytic fungi-based synthesis of quinine was published in 2002 [94]. Maehara and co-workers have found 21 endophytic fungal strains of *Cinchona ledgeriana* positive for quinine synthesis and identified them as strains of *Arthrimum*, *Fomitopsis*, *Diaporthe*, *Penicillium*, *Phomopsis*, and *Schizophyllum* [64]. Similarly, Hidayat et al. reported seven different strains of three *Fusarium* species capable of producing quinine (Table 1) [65].

2.1.10. Rohitukine

Rohitukine, a lead for the semisynthetic potential anticancer drugs flavopiridol (Sanofi-Aventis, Paris, France) and P-276-00 (Piramal Healthcare Ltd., Mumbai, India), is mainly isolated from the bark of *Dysoxylum binectariferum*. However, the removal of bark poses a threat to the survival of the source medicinal plant. Rohitukine exhibits anticancer activity through the up-regulation of p53 and caspase-9 and down-regulation of Bcl-2 protein [95]. In 2012, Kumara and his group isolated an endophyte *Fusarium proliferatum* from *D. binectariferum* that produces host-derived rohitukine [66]. Later, rohitukine-producing other species of *Fusarium* (Table 1) were also recovered from *D. binectariferum* and *Amoora rohituka* [67].

2.1.11. Sanguinarine

Sanguinarine (SA), a toxic benzophenanthridine alkaloid found in the root of *Sanguinaria canadensis* and leaves of *Macleaya cordata*, recently gained attention for its cytotoxic and anticancer activities [68]. It suppresses NF- κ B activation and induces a rapid apoptotic response via glutathione depletion, and mitochondrial damage [96]. It exhibits cytotoxicity via affecting the Na⁺-K⁺-ATPase transmembrane protein, which regulates the MAPK pathway, production of reactive oxygen species (ROS), and intracellular calcium level [28]. It also inhibits microtubule polymerization and specifically induces DNA damage in cancer cells. SA has also been produced by endophytic *F. proliferatum* isolated from leaves of *M. cordata* [68].

2.1.12. Solamargine

A well-known medicinal plant *Solanum nigrum* shows anticancer, antioxidant, antimicrobial, hepatoprotective, anti-inflammatory, antipyretic, and diuretic properties due to its flavonoid and steroidal alkaloid contents. Its dominant steroidal alkaloid solamargine has exhibited potent anticancer activity against a wide range of cancer cell lines [97]. Solamargine may induce cell apoptosis via modulating the expression of TNF receptors (TNFRs), down-regulating Bcl-2 and Bcl-xL, increasing caspase-3 activity, and causing DNA damage [98]. Interestingly, an endophytic *A. flavus* isolated from its stem produced more solamargine than the host callus culture [70].

2.1.13. Swainsonine

Swainsonine is an indolizidine alkaloid found in 'locoweeds', including *Swainsona canescens*, *Astragalus*, and *Oxytropis*. It alters glycoprotein processing by inhibiting α -mannosidase and mannosidase II and causes lysosomal storage disease [15]. Research has shown that in *Astragalus*, *Oxytropis*, and *Swainsona* species, swainsonine is produced by endophytic fungi in genera *Embellisia* and *Undifilum* [71,72,74]. Interestingly, in earlier research, plants of *Astragalus* and *Oxytropis* without endophytes were found to be swainsonine-free [99].

2.1.14. Vinblastine and Vincristine

Madagascar periwinkle (*Catharanthus roseus*) is a primary source of well-known anticancer terpenoid indole alkaloids vinblastine and vincristine. They are the second most used class of anticancer drugs in chemotherapy regimens of various malignancies such as acute lymphoblastic leukemia and neuroblastoma [100]. Alkaloid vincristine interferes with spindle formation, intracellular transport, and angiogenesis in tumor cells without affecting normal cells. For the first time in 1998, Guo et al. reported the isolation of vinblastine from an endophytic fungus *Alternaria* sp., residing in *C. roseus* [75]. The endophytic fungi *Fusarium oxysporum*, *Talaromyces radicus*, and *Eutypella* spp. from *C. roseus* produced both vinblastine and vincristine [76–79].

2.1.15. Vincamine

Indole alkaloid vincamine is one of the most important constituents of *Vinca minor* and *Nerium indicum* (apocynaceae) and is used in treating various cerebrovascular disorders such as hypertension, chronic ischemic stroke, and vascular dementia [101]. In 2011, Yin and Sun reported a vincamine-producing endophyte from the host *V. minor* [81].

2.2. Plant-Derived Coumarins (Benzopyrones) from Fungal Endophytes

Coumarins have been routinely employed as herbal remedies since the onset of herbal medicine. It was first isolated as a natural product from seeds of *Dipteryx odorata* (*Coumarouna odorata*) [102]. A total of seven medicinally important specific plant-derived coumarins are produced by fungal endophytes (Table 2).

Table 2. Plant-derived coumarins produced by endophytic fungi.

Plant-Derived Coumarins	Activities/Applications	Plant Source	Endophytic Source	Host Plant	References
Bergapten, Meranzin	Antioxidant, psoriasis treatment	<i>Balanites aegyptiaca</i> , <i>Citrus bergamia</i> , Grapefruit peel	<i>Penicillium</i> sp.	<i>Avicennia</i>	[103]
			<i>Botryodiplodia theobromae</i>	<i>Dracaena draco</i>	[104]
Isofraxidin	Anticancer, anti-obesity, cardioprotective, neuroprotective, hyper pigmentation	<i>Acanthopanax senticosus</i> , <i>Sarcandra glabra</i>	<i>Annulohypoxyylon bovei</i> var. <i>microspora</i>	<i>Cinnamomum</i> sp.	[105,106]
Marmesin	Anticancer, antihelmintic, antioxidant, antisiphilitic, purgative	<i>Ammi majus</i> , <i>Balanites aegyptiaca</i>	<i>Fusarium</i> sp.	Mangrove	[107]
			<i>Septoria nodorum</i>	Conifer	[108]
Mellein	Antibacterial, antifungal, antihepatitis c, larvicidal, phytotoxic	<i>Alibertia macrophylla</i> , <i>Litsea akoensis</i> , <i>Garcinia bancana</i> , <i>Moringa oleifera</i> , <i>Stevia lucida</i>	<i>Penicillium janczewskii</i>	<i>Prumnopitys andina</i>	[109]
			<i>Botryosphaeria mamane</i>	Anonymous	[110]
			A xylariaceous fungus	<i>Sapindus saponaria</i>	[111]
			<i>Annulohypoxyylon bovei</i> var. <i>microspora</i>	<i>Cinnamomum</i> sp.	[106]
			<i>Penicillium</i> sp., <i>Xylaria</i> sp.	<i>Alibertia macrophylla</i> , <i>Piper aduncum</i>	[112]
			<i>Annulohypoxyylon squamulosum</i>	<i>Cinnamomum</i> sp.	[113]
			<i>Nigrospora</i> sp.	<i>Moringa oleifera</i>	[114]
			<i>Arthrimum</i> (<i>Apiospora montagnei</i>)	Anonymous	[115]
			<i>Xylaria</i> sp.	<i>Garcinia</i> sp.	[116]
			<i>Pezicula</i> sp.	<i>Forsythia viridissima</i>	[117]
<i>Xylaria cubensis</i>	<i>Litsea akoensis</i>	[118]			

Table 2. Cont.

Plant-Derived Coumarins	Activities/Applications	Plant Source	Endophytic Source	Host Plant	References
Scopoletin, Umbelliferone	Antifungal, antioxidant, anti-inflammatory	<i>Artemisia scoparia</i> , <i>Scopolia carniolica</i> (syn. <i>Scopolia japonica</i>), <i>Viburnum prunifolium</i>	<i>Penicillium</i> sp.	<i>Avicennia</i>	[103]

2.2.1. Bergapten and Meranzin

Furocoumarin bergapten (5-methoxypsoralen) from *Citrus bergamia* and *Balanites aegyptiaca* is a potential photosensitizing drug in the oral photochemotherapy of psoriasis. Bergapten forms a stable combination with pyrimidine bases causing DNA damage and phosphatase and tensin homolog (PTEN)-mediated induced autophagy, indicating anti-cancer activity [119]. Meranzin exhibits an antidepressant effect through regulation of the α 2-adrenoceptor [120]. Meranzin along with bergapten is also found in grapefruit peels [121]. Both of the compounds are also produced by endophytic fungi *Penicillium* sp., *Botryodiplodia theobromae*, and *Alternaria brassicae* [103,104].

2.2.2. Isofraxidin

Isofraxidin is a coumarin compound produced in the Siberian ginseng (*Acanthopanax senticosus* or *Eleutherococcus senticosus*) and *Apium graveolens*. Isofraxidin mainly regulates lipid metabolism and protects from related disorders by reducing triglyceride accumulation, TNF- α release, and ROS activation, enhancing the phosphorylation of AMPK α and acetyl coenzyme A carboxylase (ACC). It also reduces hepatic expression of fatty acid synthase (FAS) and 3-hydroxy-3-methylglutaryl-CoA synthase 2 (HMGCoA), inhibiting lipogenesis. Additionally, isofraxidin shows anti-inflammatory activity by significantly depleting infiltrating inflammatory cells (F4/80+ Kupffer cells, and CD68+ macrophages) and inflammatory cytokines (TNF- α and IL-6) in liver cells. Moreover, the anti-inflammatory activity of isofraxidin is correlated with the down-regulation of toll-like receptor 4 (TLR4) and NF- κ B expression [122]. Isofraxidin bioactivity as a potent hyperpigmentation agent is exerted by increased melanin synthesis via stimulated tyrosinase activity, increased expression of tyrosinase, and melanogenesis regulator microphthalmia-associated transcription factor (MITF) in melanocytes [123]. The cytotoxic effects of isofraxidin on cancer cells is exerted via inhibition of AKT kinase and increase in caspase-3, caspase-9, and Bax/Bcl-2 levels. Isofraxidin has also shown anti-hypertension effects via inhibiting the activity of angiotensin I converting enzyme (ACE). Isofraxidin protects axons and dendrites against amyloid β (A β 25–35) and inhibits neuron-degenerating enzyme monoamine oxidase B [124].

2.2.3. Marmesin

Marmesin (furanocoumarins) was first reported from fruits of *Ammi majus* and later from *Balanites aegyptiaca*, which is a folkloric medicinal plant with purgative, antihelmintic, and antisyphilitic properties [119,125]. It is also synthesized by endophytic *Fusarium* sp. isolated from a mangrove plant [107].

2.2.4. Mellein

Dihydroisocoumarin mellein derives its name from a strain of *Aspergillus melleus*, which is the first reported source of mellein [126]. Later, this compound was found in plants such as *Moringa* and *Stevia* [127,128]. Mellein has exhibited antimicrobial and anti-schistosomiasis activities [114,115]. Mellein has been reported from endophytic fungal

species *Septoria nodorum* in 1995 by Findlay et al. followed by dozens of similar reports as listed in Table 2 [108].

2.2.5. Scopoletin and Umbelliferone

Scopoletin (6-methoxy-7-hydroxycoumarin) is a coumarin with antifungal, anti-acetylcholinesterase (AChE), and antitumor properties. Scopoletin inhibits cancer cell proliferation by inducing apoptosis via reducing the protein content and decreasing the acid phosphatase (ACP) activity level [129,130]. Umbelliferone (7-hydroxycoumarin), distributed within the Rutaceae and Apiaceae (Umbelliferae) families, is a fluorescing compound and used as a sunscreen agent. It shows antioxidant, anti-inflammatory, anti-hyperglycemic, anti-tumor, and antimicrobial activities. Umbelliferone exhibits anticancer activity via inducing apoptosis and cell cycle arrest [131].

2.3. Plant-Derived Flavonoids from Fungal Endophytes

Flavonoids are pigments of edible plants consisting of two benzene rings at either side of a three-carbon ring. Multiple substitutions in this basic structure produce several classes of derivatives, such as flavones, isoflavones, flavonols, flavanones, catechins, and anthocyanins. We found 12 different biologically active plant-derived flavonoids (Table 3) recovered from fungal endophytes and important flavonoids are described below.

Table 3. Plant-derived flavonoids produced by endophytic fungi.

Plant-Derived Flavonoids	Activities/Applications	Plant Source	Endophytic Source	Host Plant	References
Apigenin	Antibacterial, anticancer, antioxidant, antihyperglycaemic, lipid peroxidation, sedative, thyroid dysfunction	<i>Cajanus cajan</i> , <i>Cephalotaxus harringtonia</i> , <i>Matricaria chamomilla</i> , vegetables	<i>Colletotrichum</i> sp.	<i>Ginkgo biloba</i>	[132–134]
			<i>Chaetomium globosum</i>	<i>Cajanus cajan</i>	[135]
			<i>Paraconiothyrii mvariabile</i>	<i>Cephalotaxus harringtonia</i>	[136]
Cajanol	Anticancer, antimicrobial, antiplasmodial	<i>Cajanus cajan</i>	<i>Hypocreaxii</i>	<i>Cajanus cajan</i>	[137]
Chalcone	Antibacterial, antifungal, antitumor, anti-inflammatory	<i>Cleistocalyx operculatus</i> , Members of Leguminosae, Asteraceae, Moraceae	<i>Ceriporia lacerata</i>	<i>Cleistocalyx operculatus</i> (syns. <i>Eugenia operculata</i> , <i>Syzygium operculatum</i>)	[138]
Chrysin	Antiaging, anticonvulsant, antidiabetic, anti-inflammatory, antimicrobial, anxiolytic, hepatoprotective	<i>Passiflora incarnata</i>	<i>Alternaria alternata</i> , <i>Colletotrichum capsici</i> , <i>Colletotrichum taiwanense</i>	<i>Passiflora incarnata</i>	[139]
Curcumin	Anti-inflammatory, antioxidant, antitumor	<i>Curcuma</i> spp.	<i>Chaetomium globosum</i>	<i>Curcuma wenyujin</i>	[140]
			Anonymous	<i>Curcuma wenyujin</i>	[141]
Kaempferol	Antibacterial, antidiabetic, anti-inflammatory, antioxidant, antitumor	Fruits, vegetables, medicinal herbs	<i>Annulohypoxyylonboveri</i> var. <i>microspora</i> , <i>Annulohypoxyylon squanulosum</i>	<i>Cinnamomum</i> sp.	[106,113]
			<i>Fusarium chlamydosporum</i>	<i>Tylophora indica</i>	[142]
			<i>Mucor fragilis</i>	<i>Podophyllum hexandrum</i>	[143]

Table 3. Cont.

Plant-Derived Flavonoids	Activities/Applications	Plant Source	Endophytic Source	Host Plant	References
Luteolin	Anti-inflammatory, antioxidant, immunomodulatory	Fruits, vegetables, medicinal herbs	<i>Annulohyphoxylon boveri</i> var. <i>microspora</i>	<i>Cinnamomum</i> sp.	[106]
			<i>Aspergillus fumigatus</i>	<i>Cajanus cajan</i>	[144]
Quercetin	Anticancer, anti-inflammatory antioxidant	Fruits, vegetables	<i>Aspergillus nidulans</i> , <i>Aspergillus oryzae</i>	<i>Ginkgo biloba</i>	[145]
			<i>Annulohyphoxylon squamulosum</i>	<i>Cinnamomum</i> sp.	[113]
			<i>Nigrospora oryzae</i>	<i>Loranthus micranthus</i>	[146]
Rotenone	Insecticide, pesticide, piscicide	<i>Derris elliptica</i>	<i>Penicillium</i> sp.	<i>Derris elliptica</i>	[147]
Rutin	Antioxidant, cardioprotective, neuroprotective	<i>Aegle marmelos</i> , <i>Ginkgo biloba</i> , <i>Nerium oleander</i> , <i>Pteris multifida</i> , fruits, vegetables	Anonymous	<i>Pteris multifida</i>	[148]
			<i>Chaetomium</i> sp.	<i>Nerium oleander</i>	[149]
			<i>Xylaria</i> sp.	<i>Ginkgo biloba</i>	[150]
			<i>Aspergillus flavus</i>	<i>Aegle marmelos</i>	[151]
Silymarin	Anticancer, antioxidant, anti-inflammatory, cardioprotective, hepatoprotective	<i>Silybum marianum</i>	<i>Aspergillus iizukae</i>	<i>Silybum marianum</i>	[152]
Vitexin	Antioxidant, antitumor, neuroprotective	<i>Cajanus cajan</i> , <i>Vitex agnus-castus</i>	<i>Colletotrichum</i> sp.	<i>Ginkgo biloba</i>	[134]
			<i>Dichotomopilus funicola</i>	<i>Cajanus cajan</i>	[153]

2.3.1. Apigenin

Apigenin, amply present in *Matricaria* spp. and vegetables, has anti-inflammatory, antioxidant, and anticancer properties. Apigenin inhibits the proliferation of malignant cancer cells causing G₂-M arrest by inhibition of the mitotic kinase activity of p34^{cde2} and perturbation of cyclin B1 levels [132,154]. It is also a ligand for the central benzodiazepine receptors exerting anxiolytic and sedative effects [155]. Apigenin activates different anti-inflammatory pathways, including p38/MAPK and phosphatidylinositol 3-kinase (PI3K)/AKT, to exert its anti-inflammatory effect. Further, it prevents the I κ B degradation and nuclear translocation of the NF- κ B, and reduces cyclooxygenase (COX)-2 activity. Additionally, apigenin up-regulates the expression of anti-oxidant enzymes such as glutathione (GSH)-synthase, catalase, and superoxide dismutase (SOD) to counteract cellular oxidative stress. Its neuroprotective effect is exhibited by the lowering of β -amyloids and restoring the ERK/cyclic AMP response element-binding protein (CREB)/brain-derived neurotrophic factor (BDNF) pathway [156]. Apigenin also regulates hyperglycemia, thyroid dysfunction, and lipid peroxidation [133]. A fungal endophyte *Chaetomium globosum*, isolated from *Cajanus cajan*, produced apigenin with good antioxidant activities [135]. Its glycosidic derivatives, namely apigenin-5-O- α -L-rhamnopyranosyl-(1 \rightarrow 3)- β -D-glucopyranoside and euryanoside (apigenin-5-O- α -L-rhamnopyranosyl-(1 \rightarrow 2)-(6''-O-acetyl)- β -D-glucopyranoside), were detected in *Paraconiothyrium variabile*, which is an endophytic fungus in the Japanese plum yew (*Cephalotaxus harringtonia*) from which these compounds had previously been reported [136].

2.3.2. Cajanol

Cajanol (phytoalexin) is an isoflavone from roots of *C. cajan* displaying anticancer, antimicrobial, and antiplasmodial activities. Cajanol arrests the cell cycle in the G₂/M phase and induces apoptosis via the ROS-mediated mitochondria-dependent pathway [157]. Endophytic strains of *Hypocrea lixii* from roots of *C. cajan* have also been reported to produce cajanol in aqueous cultures with anticancer activity [137].

2.3.3. Chrysin

The flavonoid chrysin is found in leaves of *P. incarnata* and synthesized by foliar endophytes *A. alternata*, *Colletotrichum capsici*, and *Colletotrichum taiwanense*. It has shown promising biological activities, including antibacterial, anti-inflammatory, antidiabetic, anxiolytic, hepatoprotective, anti-aging, and anticancer effects [139].

2.3.4. Curcumin

Curcumin is the major active principal of *Curcuma* spp. It shows strong anti-inflammatory and antioxidant activities via the downregulation of COX-2, lipoxygenase, TNF- α , IL-1, -2, -6, -8, and Janus kinases. Curcumin anticancer activity involves cell cycle arrest via inhibition of cyclin D1 and CDK4, and induction of apoptotic signals via the up-regulation of Fas, FasL, and DR₅ expression, p-53 mediated activation of caspase, and inhibition of TNF- α -induced activation of NF- κ B [158]. A recent report has suggested curcumin as a potent epigenetic modulator with activities like inhibition of DNA methyltransferases (DNMTs), regulation of histone acetyltransferases (HATs) and histone deacetylases (HDACs), regulation of microRNAs (miRNA). It also interacts with DNA and transcription factors [159]. Curcumin has been isolated from fungal endophytes *Chaetomium globosum* and an unidentified isolate [140,141].

2.3.5. Kaempferol

Kaempferol is a potent antioxidant, anticancer, cardioprotective, neuroprotective, hepatoprotective, and antidiabetic compound found in fruits and vegetables. It blocks the expression of inflammatory cytokines (IL-1B and TNF- α), COX-2 protein, and inducible NO synthase (iNOS). Kaempferol inhibits various cancer cells by arresting cell cycle at the G₂/M phase, targeting several signaling pathways (MAPK/ERK and PI3K/AKT) that are essential for the survival of cancer cells and modulating expression of epithelial-mesenchymal transition (EMT)-related markers. It prevents the EGF-induced activation of activator protein 1 (AP-1) and NF- κ B, and phosphorylation of AKT. It enhances cyclin-dependent kinase inhibitor 1A (CDKN1A) levels via the reduced expression of c-Myc and enhanced level of p53 protein [160,161]. Kaempferol is thereby used as a potent chemopreventive agent in cancer treatment. Endophytic *Fusarium chlamydosporum* as well as its host *Tylophora indica* both can produce kaempferol [142]. It is also produced by some other endophytes (Table 3).

2.3.6. Luteolin

Luteolin is a plant metabolite with reputed antioxidant, anti-inflammatory, anticancer, and antidiabetic properties. Its anticancer property is manifested via cell cycle arrest in S phase, modulation in ROS levels, inhibition of topoisomerases type I and II, reduction of NF- κ B and AP-1 activity, stabilization of p53, and inhibition of PI3K, STAT3, insulin-like growth factor 1 receptor (IGF1R), and HER2 [162]. Luteolin is a better inhibitor of alpha-glucosidase than the widely prescribed drug acarbose, suggesting its role in reducing high blood sugar levels [163]. It has also been reported as a secondary metabolite of some endophytic fungal strains (Table 3).

2.3.7. Quercetin

Quercetin is a red pigment with antioxidant, anti-inflammatory, anticancer, antiviral, antidiabetic, cardiovascular, and neuroprotective properties that is widely distributed in plants. Quercetin causes cell cycle arrest in the S phase and activates apoptosis in cancer

cells [164]. Quercetin along with vitamin C may be used for the prevention of severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2/COVID-19) in high-risk populations [165]. Its antidiabetic activity is exhibited by induced insulin sensitivity and glucose metabolism. The cardiovascular effects of quercetin are exerted by its inhibitory effect on the angiotensin-converting enzyme and by activating Na⁺-K⁺-2Cl⁻ cotransporter 1 (NKCC1) in renal epithelial cells [166]. The mechanism behind the neuroprotective effect of quercetin may involve mitigating oxidative stress via induction of nuclear erythroid 2-related factor 2 (Nrf2)/ antioxidant response element (ARE) and antioxidant paraoxonase 2 (PON2) [167]. Recently, three quercetin compounds were extracted from the endophytic fungus *Nigrospora oryzae* isolated from leaves of the Nigerian mistletoe *Loranthus micranthus* [146].

2.3.8. Rutin

Rutin, a glycoside of the flavonoid quercetin with powerful antioxidant, anti-inflammatory, anticancer, and promising neuroprotective properties is found in vegetables and fruits. The anti-inflammatory and antioxidant activities of rutin involves inhibition of expression of COX-2 and iNOS via inhibition of p38 MAPK and c-Jun N-terminal kinase (JNK). Rutin decreases Bcl-2 expression, Bcl-2/Bax ratio, MYCN mRNA levels, and the secretion of TNF- α , demonstrating its anticancer property [168]. Its neuroprotective mechanisms include reduction of pro-inflammatory cytokines, improved antioxidant enzyme activities, activation of MAPK cascade, up-regulation of the ion transport and antiapoptotic genes, and restoration of the activities of mitochondrial complex enzymes [169]. Rutin has also been produced by several endophytic fungi, as listed in Table 3.

2.3.9. Silymarin

Silymarin, a bioactive natural compound found in fruits of milk thistle (*Silybum marianum*), has cardioprotective, hepatoprotective, antioxidant, immunomodulatory, anti-inflammatory, antihepatic, and antimetastatic activities [170]. The hepatoprotective property of silymarin is accomplished via an increase in glutathione level, inhibition of lipid peroxidation, activation of antioxidant defense, and translational activities in hepatic cells [171]. Its anticancer activity is related to the modulation of NF- κ B, suppression of EGFR-MAPK/ERK1/2 and IGF1R signaling, up-regulation of tumor-suppressor genes p53 and p21^{CIP1}. Similarly, its antiangiogenic activity is linked to suppression of both vascular endothelial growth factor (VEGF) and MMP-2 [172,173]. Endophytic silymarin for the first time has been reported from the strains of *Aspergillus iizukae* isolated from the leaves and stems of *S. marianum* [152].

2.3.10. Vitexin

C-glycosyl flavonoid vitexin has recently received increased attention due to its wide range of pharmacological effects including anticancer (as hypoxia inducible factor (HIF)-1 α inhibitor), analgesic (via targeting TRPV1), antioxidant, hypotensive, neuroprotective, and antidiabetic effects [174]. It is synthesized by plants such as *C. cajan*, *Ficus deltoidea*, *Passiflora incarnata*, *Vitex agnus-castus*, and endophytic fungi such as *Colletotrichum* sp. from *G. biloba* [134] and *Dichotomopilus funicola* of *C. cajan* [153].

2.4. Plant-Derived Lignans from Fungal Endophytes

Lignans are secondary metabolites with a plethora of biological activities, making them noteworthy in several lines of research. Out of a total of seven medicinally important plant-derived lignans that have been secreted by endophytes (Table 4), one is described below.

Table 4. Plant-derived lignans produced by endophytic fungi.

Plant-Derived Lignans	Activities/Applications	Plant Source	Endophytic Source	Host Plant	References
Coniferin	Antidiabetic	<i>Angelica archangelica</i> , Conifers	Members of xylariaceae	<i>Angelica archangelica</i>	[175]
Phillyrin	Antioxidant, antidiabetic, anti-inflammatory, anti-obesity, antipyretic	<i>Forsythia suspensa</i> , <i>Phyllirea</i>	<i>Colletotrichum gloeosporioides</i>	<i>Forsythia suspensa</i>	[176,177]
Podophyllotoxin	Antitumor, antiviral	<i>Diphylleia</i> sp., <i>Dysosma</i> sp., <i>Juniperus</i> sp., <i>Podophyllum</i> spp.	<i>Alternaria</i> sp., <i>Penicillium</i> spp.	<i>Podophyllum hexandrum</i>	[178]
			<i>Monilia</i> sp., <i>Penicillium</i> sp.	<i>Dysosma veitchii</i>	[178]
			<i>Penicillium</i> sp.	<i>Diphylleia sinensis</i>	[178]
			<i>Penicillium implicatum</i>	<i>Diphylleia sinensis</i>	[179]
			<i>Alternaria</i> sp.	<i>Juniperus vulgaris</i>	[180]
			<i>Phialocephala fortinii</i>	<i>Podophyllum peltatum</i>	[181]
			<i>Trametes hirsuta</i>	<i>Podophyllum hexandrum</i>	[182]
			<i>Alternaria neesex</i>	<i>Podophyllum hexandrum</i>	[183]
			<i>Fusarium oxysporum</i>	<i>Juniperus recurva</i>	[184]
			<i>Aspergillus fumigatus</i>	<i>Juniperus communis</i>	[185]
			<i>Fusarium solani</i>	<i>Podophyllum hexandrum</i>	[186]
			<i>Mucor fragilis</i>	<i>Podophyllum hexandrum</i>	[143]
			<i>Phialocephala podophylli</i>	<i>Podophyllum peltatum</i>	[187]
<i>Alternaria tenuissima</i>	<i>Podophyllum emodi</i>	[188]			
<i>Fusarium</i> sp.	<i>Dysosma versipellis</i>	[189]			
Sesamin, Syringaresinol, Ketopinoresinol	Antioxidant, anti-inflammatory	<i>Cinnamomum cassia</i>	<i>Annulohypoxyylon ilanense</i>	<i>Cinnamomum</i> sp.	[190]
Syringin	Antidiabetic	<i>Syringa vulgaris</i> , <i>Eleutherococcus senticosus</i> , <i>Magnolia sieboldii</i> , <i>Musa paradisiaca</i>	Members of xylariaceae	<i>Syringa vulgaris</i>	[175,191]

Podophyllotoxin

Podophyllotoxin (podofilox), an aryl tetralin lactone lignan of medicinal plant *Podophyllum* sp., is an important anticancer and antiviral agent. It is also found in *Diphylleia*, *Dysosma*, and *Juniperus*. It has been used as the lead for the chemical synthesis of the many use-

ful anticancer drugs such as etoposide, teniposide, and etopophos phosphate [184,185]. Podophyllotoxin is an anti-tubulin agent that destabilizes microtubules. Its derivatives inhibit the topoisomerase II enzyme, which is required to unwind the double helix of DNA, preventing mitosis in late S/early G₂ phase [192]. For the first time, Yang et al. in 2003 reported the podophyllotoxin producing endophytic fungi (Table 4) from *P. hexandrum*, *Diphylleia sinensis*, and *Dysosma veitchii* [178]. Puri et al. in 2006 reported a fungal endophyte *Trametes hirsuta* from rhizomes of *P. hexandrum* that efficiently produces podophyllotoxin and other related aryl tetralin lignans with potent anticancer properties [182]. Later, several other endophytic fungi such as *Phialocephala fortinii* isolated from the rhizomes of *Podophyllum peltatum*, *Alternaria* sp. isolated from *Juniperus vulgaris*, and *P. hexandrum*, *F. oxysporum* isolated from *Juniperus recurva*, and *A. fumigatus* isolated from *Juniperus communis* have been reported as alternative sources for podophyllotoxin [180,181,183–185]. Recently, *A. tenuissima*, a fungal endophyte from the roots of *Podophyllum emodi*, and *Fusarium* sp. from *Dysosma versipellis* showed the presence of podophyllotoxin in their secondary metabolite analysis [188,189]. In total, podophyllotoxin has been isolated from 17 endophytic fungal species collected from 10 different host plant species, as listed in Table 4.

2.5. Plant-Derived Saponins from Fungal Endophytes

Saponins are known to occur in many taxonomically unrelated plants, but there is evidence that they are also produced by endophytic fungi (Table 5). We found three specific and several other plant-derived saponins that have been reported from endophytic fungi.

Table 5. Plant-derived saponins produced by endophytic fungi.

Plant-Derived Saponins	Activities/Applications	Plant Source	Endophytic Source	Host Plant	References
Diosgenin	Anti-inflammatory, antitumor, cardiovascular protection	<i>Dioscorea</i> spp.	<i>Paecilomyces</i> sp.	<i>Paris polyphylla</i> var. <i>yunnanensis</i>	[193]
			<i>Cephalosporium</i> sp.	<i>Paris polyphylla</i> var. <i>yunnanensis</i>	[194]
			<i>Fusarium</i> sp.	<i>Dioscorea nipponica</i>	[195]
Ginsenoside	Anti-inflammatory, antioxidation, antitumor	<i>Panax</i>	<i>Camarosporium</i> sp., <i>Dictyochaeta</i> sp., <i>Penicillium</i> sp.	<i>Aralia elata</i>	[196]
			<i>Aspergillus</i> sp., <i>Fusarium</i> sp., <i>Verticillium</i> sp.	<i>Panax ginseng</i>	[197]
			<i>Aspergillus</i> sp., <i>Fusarium</i> sp.	<i>Panax notoginseng</i>	[198]
Gymnemagenin	Antidiabetic	<i>Gymnema sylvestre</i>	<i>Penicillium oxalicum</i>	<i>Gymnema sylvestre</i>	[199]
Other saponins	Cardiovascular disease	<i>Gynostemma pentaphyllum</i> , <i>Manilkara zapota</i> , <i>Sapindus</i> sp., <i>Saponaria</i> sp.	<i>Aspergillus niger</i> , <i>F. oxysporum</i>	<i>Crotalaria pallida</i>	[200]
			<i>Alternaria alternata</i> , <i>Aspergillus niger</i> , <i>Penicillium</i> sp.	<i>Loranthus</i> sp.	[201]
			<i>Alternaria alternata</i> , <i>Aspergillus flavus</i> , <i>Aspergillus niger</i> , <i>Colletotrichum gleosporioides</i> , <i>Trichoderma</i> sp.	<i>Tabebuia argentea</i>	[202]
			<i>Aspergillus</i> sp.	<i>Salvadora oleoides</i>	[203]

Table 5. Cont.

Plant-Derived Saponins	Activities/Applications	Plant Source	Endophytic Source	Host Plant	References
			<i>Aspergillus</i> sp.	<i>Justicia beddomei</i>	[204]
			<i>Cochliobolus lunatus</i> (anamorph <i>Curvularia lunata</i>)	<i>Boswellia ovalifoliolata</i>	[205]
			<i>Monochaetia karstenii</i> (syn. <i>Pestalotiopsis maculans</i>), <i>Phyllosticta</i> sp.	<i>Shorea thumbugaia</i>	[205]
			<i>Aspergillus neoniveus</i> (syn. <i>Fennellia nivea</i>)	<i>Typhonium divaricatum</i>	[206]
			<i>Alternaria alternata</i> , <i>Aspergillus flavus</i> , <i>Aspergillus niger</i> , <i>Cladosporium</i> sp., <i>Penicillium</i> sp., <i>Phomopsis</i> sp., <i>Trichoderma</i> sp.	<i>Aegle marmelos</i>	[207]
			<i>Aspergillus niger</i> , <i>Aspergillus</i> sp., <i>Aspergillus terreus</i> , <i>Aspergillus tubingensis</i> , <i>Coprinopsis cinerea</i> , <i>Curvularia lunata</i> , <i>Fusarium</i> sp.	<i>Eugenia jambolana</i>	[208]
			<i>Aspergillus awamori</i> , <i>Colletotrichum gleosporioides</i>	<i>Rauwolfia serpentina</i>	[209]

Diosgenin

The anti-inflammatory and anticancer agent diosgenin is primarily obtained from *Dioscorea zingiberensis*. Its anti-inflammatory activity is exerted via reduction in the levels of several inflammatory mediators, including NO and IL-1 and -6, inhibition of the MAPK/AKT/NF- κ B signaling pathway, and ROS production. Diosgenin anticancer effects have been linked to p53 activation, immune modulation, cell cycle arrest, modulation of caspase-3 activity, and activation of STAT3 signaling pathway [210]. Considering the depleting natural populations and requirement of a long period of rhizome maturation of its primary source *Dioscorea zingiberensis*, endophytes might be suitable alternatives to produce diosgenin. Zhou et al. in 2004 first reported *Paecilomyces* sp. residing in *Paris polyphylla* var. *yunnanensis* as an adiosgenin-producing endophytic fungus [193]. Later, an endophytic strain of *Fusarium* sp. from *Dioscorea nipponica* was also been reported for enhanced production of diosgenin in its liquid cultures when supplemented with the rhizome extract of its host plant [195].

2.6. Plant-Derived Terpenes from Fungal Endophytes

Table 6 lists 17 specific plant-derived terpenes produced by fungal endophytes with some of them detailed below.

Table 6. Plant-derived terpenes produced by endophytic fungi.

Plant-Derived Terpenes	Activities/Applications	Plant Source	Endophytic Source	Host Plant	References
Agathic acid	Abortifacient, anti-inflammatory, anticancer, trypanocidal	<i>Agathis</i> spp., <i>Copaifera</i> spp., <i>Juniperus osteosperma</i>	<i>Botryosphaeria</i> sp.	<i>Maytenus hookeri</i>	[211–213]
			<i>Bionectria</i> sp.	<i>Raphia taedigera</i>	[214]
			<i>Fusarium</i> sp.	<i>Santalum album</i>	[215]
Artemisinin	Antimalarial	<i>Artemisia</i> spp.	Anonymous	<i>Artemisia indica</i>	[216]
Asiaticoside	Antidermatitic, anti-inflammatory, antioxidant, immunomodulatory	<i>Centella asiatica</i>	<i>Colletotrichum gloeosporioides</i>	<i>Centella asiatica</i>	[217]
Azadirachtin	Hepatoprotective, insecticidal	<i>Azadirachta indica</i>	<i>Penicillium</i> (<i>Eupenicillium</i>) <i>parvum</i>	<i>Azadirachta indica</i>	[218]
Bilobalide	Neuroprotective,	<i>Ginkgo biloba</i>	<i>Pestalotiopsis uvicola</i>	<i>Ginkgo biloba</i>	[219]
Borneol	Antiapoptotic, anti-inflammatory, antioxidant, neuroprotective	<i>Cinnamomum camphora</i> var. <i>borneol</i>	<i>Cochliobolus nisikadoi</i>	<i>Cinnamomum camphora</i> var. <i>borneol</i>	[220]
Camphor	Antimicrobial, topical skin preparations	<i>Cinnamomum camphora</i>	<i>Nodulisporium</i> sp.	<i>Lagerstroemia loudoni</i>	[221]
			<i>Hypoxyylon</i> sp., <i>Nodulisporium</i> sp.	<i>Persea indica</i>	[222]
			<i>Nodulisporium</i> sp.	<i>Lagerstroemia loudoni</i>	[221]
			<i>Nodulisporium</i> sp.	<i>Thelypteris angustifolia</i>	[223]
			<i>Nodulisporium</i> sp.	<i>Cassia fistula</i>	[224]
Cineole (Eucalyptol)	Antimicrobial, respiratory illness	<i>Eucalyptus</i> spp.	<i>Annulohypoxyylon</i> sp.	<i>Neolitsea pulchella</i>	[225]
			<i>Nodulisporium</i> sp.	<i>Lagerstroemia loudoni</i>	[221]
			<i>Nodulisporium</i> sp.	<i>Thelypteris angustifolia</i>	[223]
			<i>Nodulisporium</i> sp.	<i>Cassia fistula</i>	[224]
Dihydrocumambrin	Antibacterial, cytotoxic	<i>Glebionis coronaria</i> (syn. <i>Chrysanthemum coronarium</i>)	<i>Botryodiplodia theobromae</i>	<i>Dracaena draco</i>	[104]
Ginkgolide	Antiallergic, anti-inflammatory	<i>Ginkgo biloba</i>	<i>Fusarium oxysporum</i>	<i>Ginkgo biloba</i>	[226]
Isocupressic acid	Abortifacient	Conifers	<i>Botryosphaeria</i> sp.	<i>Maytenus hookeri</i>	[212,213]
Loliolide	Herbivore resistance	<i>Lolium perenne</i>	<i>Annulohypoxyylon ilanense</i>	<i>Cinnamomum</i> sp.	[227]
			<i>Alternaria</i> , <i>Aspergillus</i> , <i>Beauveria</i> , <i>Epicoccum</i> , <i>Fusarium</i> , <i>Gelasinospora</i> , <i>Geotrichum</i> , <i>Phoma</i> , <i>Phomopsis</i>	<i>Taxus baccata</i>	[228]
Taxane (other than taxol)	Anticancer	<i>Taxus</i> spp.	<i>Cladosporium langeronii</i> , <i>Phomopsis</i> sp.	<i>Wollemia nobilis</i>	[229]

Table 6. Cont.

Plant-Derived Terpenes	Activities/Applications	Plant Source	Endophytic Source	Host Plant	References
			<i>Taxomyces andreanae</i>	<i>Taxus brevifolia</i>	[11]
			<i>Taxomyces</i> sp.	<i>Taxus yunnanensis</i>	[230]
			<i>Pestalotiopsis microspora</i>	<i>Taxodium distichum</i>	[231]
			<i>Alternaria</i> sp., <i>Pestalotiopsis microspora</i>	<i>Taxus cuspidata</i>	[232]
			<i>Fusarium lateritium</i> , <i>Monochaetia</i> sp., <i>Pestalotia bicilia</i>	<i>Taxus baccata</i>	[232]
			<i>Pithomyces</i> sp.	<i>Taxus sumatrana</i>	[232]
			<i>Pestalotiopsis microspora</i>	<i>Taxus wallichiana</i>	[233]
			<i>Pestalotiopsis guepinii</i>	<i>Wollemia nobilis</i>	[234]
			<i>Periconia</i> sp.	<i>Torreyagrandifolia</i>	[235]
			<i>Seimatoantlerium nepalense</i>	<i>Taxus wallichiana</i>	[236]
			<i>Alternaria</i> sp., <i>Pestalosiopsis</i> sp.	<i>Ginkgo biloba</i>	[237]
			<i>Penicillium raistrickii</i>	<i>Taxus brevifolia</i>	[238]
			<i>Tubercularia</i> sp.	<i>Taxus chinensis</i> var. <i>mairei</i>	[239]
			<i>Stegolerium kukenani</i>	<i>Kukenan tepuis</i> , <i>Roraima</i>	[240]
			<i>Taxomyces</i> sp.	<i>Taxus</i> sp.	[241]
			<i>Sporormia minima</i> , <i>Trichothecium</i> sp.	<i>Taxus wallichiana</i>	[242]
			<i>Nodulisporium sylviforme</i>	<i>Taxus cuspidata</i>	[243]
			Anonymous	<i>Taxus chinensis</i> var. <i>mairei</i>	[244]
			<i>Botrytis</i> sp.	<i>Taxus chinensis</i> var. <i>mairei</i>	[245]
			<i>Penicillium</i> sp.	<i>Taxus yunnanensis</i>	[246]
			<i>Fusarium mairei</i>	<i>Rhizophora annamalayana</i>	[247]
			<i>Phyllosticta</i> sp.	<i>Ocimum basilicum</i>	[248]
			<i>Alternaria alternata</i> , <i>Ectostromasp.</i> , <i>Fusarium mairei</i> , <i>Ozoniumsp.</i> , <i>Papulaspora</i> sp.	<i>Taxus chinensis</i> var. <i>mairei</i>	[249]
			<i>Fusarium solani</i>	<i>Taxus celebica</i>	[250]
Taxol	Anticancer	<i>Taxus brevifolia</i>			

Table 6. Cont.

Plant-Derived Terpenes	Activities/Applications	Plant Source	Endophytic Source	Host Plant	References
			<i>Pestalotiopsis pauciseta</i>	<i>Cardiospermum helicacabum</i>	[251]
			<i>Bartalinia robillardoides</i>	<i>Aegle marmelos</i>	[252]
			<i>Colletotrichum gloeosporioides</i>	<i>Justicia gendarussa</i>	[253]
			<i>Fusarium</i> sp.	<i>Taxus wallichiana</i>	[254]
			<i>Phyllosticta citricarpa</i>	<i>Citrus medica</i>	[255]
			<i>Phyllosticta melochiae</i>	<i>Melochia corchorifolia</i>	[256]
			<i>Phyllosticta spinarum</i>	<i>Cupressus</i> sp.	[257]
			<i>Fusarium arthrosporioides</i>	<i>Taxus cuspidata</i>	[258]
			<i>Aspergillus fumigatus</i>	<i>Podocarpus</i> sp.	[259]
			<i>Botryodiplodia theobromae</i>	<i>Taxus baccata</i>	[260]
			<i>Botrytis</i> sp.	<i>Taxus cuspidata</i>	[261]
			<i>Fusarium solani</i>	<i>Taxus chinensis</i>	[262]
			<i>Chaetomella raphigera</i>	<i>Terminalia arjuna</i>	[263]
			<i>Pestalotiopsis terminaliae</i>	<i>Terminalia arjuna</i>	[264]
			<i>Phomopsis</i> sp.	<i>Ginkgo biloba</i>	[265]
			<i>Phomopsis</i> sp.	<i>Larix leptolepis</i>	[265]
			<i>Phomopsis</i> sp.	<i>Taxus cuspidata</i>	[265]
			<i>Phyllosticta dioscoreae</i>	<i>Hibiscus rosa-sinensis</i>	[266]
			<i>Aspergillus</i> sp., <i>Ceratobasidium</i> sp., <i>Cladosporium tenuissimum</i> , <i>Coniothyrium diploidiella</i> , <i>Epacris</i> sp., <i>Fusarium solani</i> , <i>Metarhizium anisopliae</i> , <i>Paraconiothyrium brasiliense</i> , <i>Pezicula</i> sp., <i>Phomopsis</i> sp., <i>Sordaria</i> sp., <i>Trichoderma</i> sp., <i>Xylaria</i> sp.	<i>Taxus chinensis</i>	[267]
			<i>Mucor rouxianus</i>	<i>Taxus chinensis</i>	[268]

Table 6. Cont.

Plant-Derived Terpenes	Activities/Applications	Plant Source	Endophytic Source	Host Plant	References
			<i>Colletotrichum gloeosporioides</i>	<i>Plumeria acutifolia</i>	[269]
			<i>Gliocladium</i> sp.	<i>Taxus baccata</i>	[270]
			<i>Pestalotiopsis</i> sp.	<i>Catharanthus roseus</i>	[271]
			<i>Aspergillus candidus</i> , <i>Cladosporium cladosporioides</i>	<i>Taxus media</i>	[272,273]
			<i>Aspergillus niger</i> var. <i>taxi</i>	<i>Taxus cuspidata</i>	[274]
			<i>Mucor</i> sp.	<i>Taxus chinensis</i> var. <i>mairei</i>	[275]
			<i>Pestalotiopsis neglecta</i> , <i>Pestalotiopsis versicolor</i>	<i>Taxus cuspidata</i>	[276]
			<i>Pestalotiopsis pauciseta</i>	<i>Tabebuia pentaphylla</i>	[277]
			<i>Lasiodiplodia theobromae</i>	<i>Morinda citrifolia</i>	[278]
			<i>Acremonium</i> sp., <i>Botryosphaeria</i> sp., <i>Fusarium</i> sp., <i>Gyromitra</i> sp., <i>Nigrospora</i> sp., <i>Penicillium</i> sp.	<i>Taxus globosa</i>	[279]
			<i>Paraconiothyrium</i> sp.	<i>Taxus media</i>	[280]
			<i>Didymostilbe</i> sp.	<i>Taxus chinensis</i> var. <i>mairei</i>	[281]
			<i>Stemphylium sedicola</i>	<i>Taxus baccata</i>	[282]
			<i>Colletotrichum gloeosporioides</i>	<i>Tectona grandis</i>	[283]
			<i>Perenniporia tephropora</i>	<i>Taxus chinensis</i> var. <i>mairei</i>	[284]
			<i>Colletotrichum gloeosporioides</i> , <i>Fusarium proliferatum</i> , <i>Guignardia mangiferae</i>	<i>Taxus media</i>	[285]
			<i>Phoma betae</i>	<i>Ginkgo biloba</i>	[286]
			<i>Alternaria</i> sp.	<i>Corylus avellana</i>	[287]
			<i>Colletotrichum gloeosporioides</i>	<i>Moringa oleifera</i>	[288]
			<i>Penicillium</i> sp.	<i>Taxus chinensis</i>	[289]
			<i>Penicillium aurantiogriseum</i>	<i>Corylus avellana</i>	[290]

Table 6. Cont.

Plant-Derived Terpenes	Activities/Applications	Plant Source	Endophytic Source	Host Plant	References
Toosendanin	Anticancer, antifeedant	<i>Melia azedarach</i>	Anonymous	<i>Melia azedarach</i>	[291,292]
Withanolide	Anticancer, cardiovascular disease, Alzheimer's disease treatment	<i>Withania</i> sp.	<i>Taleromyces pinophilus</i>	<i>Withania somnifera</i>	[293]
Xanthatin	Antitumor	<i>Xanthium</i> spp.	<i>Paecilomyces</i> sp.	<i>Panax ginseng</i>	[294,295]

2.6.1. Artemisinin

Asian plant *Artemisia annua* (sweet wormwood) has been in use for the treatment of fever since more than 2000 years. In 1971, Artemisinin, a sesquiterpene lactone with endoperoxide trioxane moiety, was isolated from the *A. annua* as its active antimalarial principle by Tu Youyou [296]. According to a WHO report, over 2010–2017, about 2.74 billion artemisinin-based combination therapies (ACTs) have been administered globally [297]. Growing evidence revealed that artemisinin and its derivatives have many more biological activities including anti-inflammatory, immunoregulatory, and anticancer activities without any risk of drug-resistant development [298]. Its antimalarial parasite activity is mediated by ROS generation, causing protein damage and compromising parasite proteasome function, inducing the endoplasmic reticulum (ER) stress response [299,300]. Iron (heme), which is a prerequisite for cancer cells multiplication, also activates an endoperoxide bond of artemisinin, creating cytotoxic/cancer-killing carbon-centered free radicals. As an alternative source, Huang et al. isolated artemisinin from an anonymous fungal isolate of *Artemisia indica* [216].

2.6.2. Bilobalide and Ginkgolides

Bilobalide and ginkgolides, two main terpenoids found in the leaves and bark of *G. biloba*, are accountable for the therapeutic implication of its whole extract [301]. Ginkgo products, including EGb-761 registered as a phytomedicine in Europe, are now among the best-selling drugs in the world with US\$ 1.26 billion worldwide sales in 2012 [302]. Widely consumed bilobalide (sesquiterpene) has neuroprotective, anti-inflammatory, and analgesic potential and inhibits the diffuse pneumonia caused by *Pneumocystis carinii* [303,304]. Bilobalide has recently been found to be an antagonistic allosteric modulator of the γ -aminobutyric acid A receptors (GABA_ARs), linking its role in improving cognitive and memory functioning domain in impaired persons [305]. Recently, *Pestalotiopsis uvicola*, a foliar endophyte of *G. biloba*, has been reported to produce bilobalide [219]. Similarly, ginkgolides are considered as possible drugs based on their key antagonistic effects on the platelet-activating factor (PAF), neuroprotective effects, and protective effects in cerebrocerebral ischemia reperfusion injuries mediated via regulation of TNF-related weak inducer of apoptosis (TWEAK)/ fibroblast growth factor-inducible molecule 14 (Fn14) signaling pathway [301,306,307]. Ginkgolides have also been found in the fermentation products of an endophytic strain of *F. oxysporum* recovered from the root bark of *G. biloba* [226].

2.6.3. Paclitaxel

Paclitaxel (PTX) is a highly functionalized diterpenoid taxane family compound with a four-membered oxetane ring and a C-13 ester side chain. It is used as a basic chemotherapy drug to treat several cancer types and was first extracted from medicinal plant Pacific yew (*Taxus brevifolia*) in 1971 [308]. Paclitaxel binds to the tubulin protein of mitotic spindles, making them nonfunctional. The stabilization of microtubules arrest mitosis in the M phase causes the reversal of cell cycle to the G₀ phase and induces apoptosis [309]. Two

decades after the discovery of paclitaxel ‘taxol’, the US FDA approved it for treating ovarian cancer in 1992 with its commercial sales reaching over \$3 billion in 2004 [308]. *T. andreanae* from *Taxus* spp. was the very first endophyte reported to produce paclitaxel, taxol [11]. The above revolutionary discovery was followed by similar findings from 83 different endophytic fungal species isolated from 35 different host plant species including *Taxus* and non-*Taxus* species, as listed in Table 6.

2.6.4. Toosendanin (TSN)

Triterpenoid toosendanin (TSN) is a main bioactive component of fruits and bark of traditional anthelmintic and insecticidal plants *Melia azedarach* and *Melia toosendan*. Toosendanin has antitubulinum (inhibits the botulinum neurotoxin interaction with the SNARE protein), anti-influenza (alters nuclear localization of viral polymerase PA protein), anticancer, anti-inflammatory, and analgesic (selective presynaptic blocker) efficacy [310,311]. Possible actions of TSN as an antitumor drug against a variety of cancer types involve inhibition of STAT3, an emerging target for cancer therapy, induction of estrogen receptor β (ER β) and p53 proteins, and activation of the mitochondrial apoptotic pathway [312–314]. Three unidentified endophytic fungal strains in *M. azedarach* have been reported to produce toosendanin [291,292].

2.6.5. Xanthatin

Xanthatin, a natural sesquiterpene lactone of *Xanthium* spp., has significant antimicrobial, trypanocidal, and antitumor activities. Xanthatin exerts its trypanocidal activity by inhibiting both prostaglandin E2 (PGE2) synthesis and 5-lipoxygenase activity, thereby avoiding unwanted inflammation commonly observed in trypanosomiasis. It also permanently inhibits the parasite-specific trypanothione reductase [294]. Xanthatin induces cell cycle arrest at the G₂/M checkpoint and apoptosis via disrupting the NF- κ B pathway [315]. It is also synthesized by endophytic *Paecilomyces* sp. from *Panax ginseng* [295].

2.7. Plant-Derived Quinones and Xanthenes from Fungal Endophytes

Table 7 lists 20 different plant-derived quinones and xanthenes that were reported from fungal endophytes with some important quinones described below.

Table 7. Plant-derived quinones and xanthenes produced by endophytic fungi.

Plant-Derived Quinones and Xanthenes	Activities/Applications	Plant Source	Endophytic Source	Host Plant	References
1,7-dihydroxyxanthone	Antioxidant	<i>Weddellina squamulosa</i>	<i>Penicillium</i> sp.	<i>Avicennia</i>	[103]
Anthraquinone	Anticancer, antioxidant, laxative	<i>Digitalis viridiflora</i> , <i>Rumex</i> spp.	<i>Coniothyrium</i> sp.	<i>Salsola oppositifolia</i>	[316]
			<i>Aspergillus fumigatus</i>	<i>Rumex nepalensis</i> , <i>Rumex hastatus</i>	[317]
Emodin	Antibacterial, anti-inflammatory, antitumor, immunosuppressive	<i>Hypericum perforatum</i> , <i>Polygonum cuspidatum</i> , <i>Rheum</i> spp.	<i>Penicillium janthinellum</i>	<i>Melia azedarach</i>	[318,319]
			<i>Talaromyces</i> sp.	<i>Kandelia candel</i>	[320]
			<i>Aspergillus versicolor</i>	<i>Halimeda opuntia</i>	[321]
			<i>Fusarium solani</i>	<i>Rheum palmatum</i>	[322]
			<i>Eurotium chevalieri</i>	Mangrove	[323]
Eugenitin	Glucoamylase activation	<i>Syzygium aromaticum</i>	<i>Alternaria alternata</i>	<i>Hypericum perforatum</i>	[324]
			<i>Dothideomycetes</i> sp.	<i>Leea rubra</i>	[325]

Table 7. Cont.

Plant-Derived Quinones and Xanthenes	Activities/Applications	Plant Source	Endophytic Source	Host Plant	References
Hypericin	Anti-depressant, antimicrobial, antiretroviral	<i>Hypericum perforatum</i>	<i>Chaetomium globosum</i>	<i>Hypericum perforatum</i>	[326]
			<i>Thielavia subthermophila</i>	<i>Hypericum perforatum</i>	[327]
			<i>Epicoccum nigrum</i>	<i>Hypericum perforatum</i>	[324]
Lapachol	Anticancer, antimicrobial, antiviral, anti-inflammatory, antiparasitic	<i>Tabebuia avellanedae</i>	<i>Alternaria</i> sp., <i>Alternaria alternata</i> , <i>Penicillium</i> sp.	<i>Tabebuia argentea</i>	[202]
			<i>Aspergillus niger</i>	<i>Tabebuia argentea</i>	[328]
Lawsone	Cytotoxic	<i>Lawsonia inermis</i>	<i>Gibberella moniliformis</i>	<i>Lawsonia inermis</i>	[329]
Pachybasin, Phomarin	Antibacterial, antiviral, bioagricultural agent	<i>Digitalis</i> spp., <i>Isoplexis isabelliana</i>	<i>Phoma sorghina</i>	<i>Tithonia diversifolia</i>	[330]
			<i>Coniothyrium</i> sp.	<i>Salsola oppositifolia</i>	[316]
Physcion (Parietin)	Antibiotics, antifungals, cytotoxic	<i>Hopea hainanensis</i> , <i>Rheum officinale</i>	<i>Aspergillus fumigatus</i>	<i>Cynodon dactylon</i>	[331]
			<i>Pleospora</i> sp.	<i>Imperata cylindrical</i>	[332]
			<i>Penicillium</i> sp.	<i>Hopea hainanensis</i>	[333]
			<i>Aspergillus terreus</i>	<i>Opuntia ficus-indica</i>	[334]
			<i>Cercospora</i> sp.	<i>Schisandra chinensis</i>	[335]
			<i>Eurotiumchevalieri</i>	Mangrove	[323]
			<i>Aspergillus sydowii</i>	<i>Scapania ciliata</i>	[336,337]
Pinselin (Cassiollin)	Cytotoxic	<i>Cassia occidentalis</i>	<i>Phomopsis</i> sp.	<i>Paris polyphylla</i> var. <i>yunnanensis</i>	[338]
			<i>Phomopsis amygdali</i>	<i>Paris axialis</i>	[339]
			<i>Penicillium</i> sp.	<i>Sonneratia apetala</i>	[340]
Plumbagin	Anticancer	<i>Plumbago zeylanica</i>	<i>Cladosporium delicatulum</i>	<i>Terminalia pallida</i>	[341]
Questin	Antioxidant, allelopathic, herbicide	<i>Leea rubra</i>	<i>Dothideomycete</i>	<i>Leea rubra</i>	[325]
			<i>Eurotium rubrum</i>	<i>Hibiscus tiliaceus</i>	[342]
			<i>Eurotium cristatum</i>	<i>Sargassum thunbergii</i>	[343]
			<i>Aspergillus</i> sp.	<i>Pleioblastus amarus</i>	[344]
			<i>Phoma</i> sp.	<i>Phragmites communis</i>	[345]
Questinol	Anti-inflammatory, antibacterial	<i>Cassia</i> spp., <i>Polygonum</i> spp.	<i>Eurotium rubrum</i>	<i>Hibiscus tiliaceus</i>	[342]
			<i>Penicillium glabrum</i>	<i>Punica granatum</i>	[346]
			<i>Eurotium chevalieri</i>	Mangrove	[323]

Table 7. Cont.

Plant-Derived Quinones and Xanthenes	Activities/Applications	Plant Source	Endophytic Source	Host Plant	References
Quinizarin	Cytotoxicity, antibacterial	<i>Rubia tinctorum</i>	<i>Epicoccum nigrum</i>	<i>Entada abyssinica</i>	[347]
Rhein	Anticancer, anti-inflammatory, antimicrobial, antioxidant, hepatoprotective, nephroprotective	<i>Rheum palmatum</i>	<i>Fusarium solani</i>	<i>Rheum palmatum</i>	[322]
Shikonin	Anti-inflammatory, anti-HIV, antimicrobial,	<i>Lithospermum erythrorhizon</i>	Anonymous	<i>Mammillaria hahniana</i>	[348]
			<i>Fusarium tricinctum</i>	<i>Lithospermum officinale</i>	[349]
Sterequinone C	Anti-inflammatory	<i>Stereospermum</i> spp.	<i>Penicillium</i> sp.	<i>Avicennia</i>	[103]
			<i>Paecilomyces</i> sp.	<i>Panax ginseng</i>	[295]
Tanshinone	Antibacterial, antifungal, anti-inflammatory, antihypertensive, antitumor	<i>Salvia</i> spp.	<i>Emericella foeniculicola</i>	<i>Salvia</i> spp.	[350]
			<i>Trichoderma atroviride</i>	<i>Salvia miltiorrhiza</i>	[351]
			<i>Phoma glomerata</i>	<i>Salvia miltiorrhiza</i>	[352]
			<i>Alternaria</i> sp.	<i>Salvia miltiorrhiza</i>	[353]
Torreyanic acid	Anticancer, cytotoxic	<i>Torreya taxifolia</i>	<i>Pestalotiopsis microspora</i>	<i>Torreya taxifolia</i>	[354]

2.7.1. Hypericin

Hypericin (naphthodianthrone) is a *Hypericum perforatum*-derived antidepressive, antineoplastic, antitumor, antiviral, and photosensitizer compound. Hypericin exerts its antidepressant activity by the inhibition of serotonin, norepinephrine, and dopamine reuptake, increases in IL-6 activity, and the agonist action of sigma receptors [355]. Due to preferential accumulation in neoplastic cells, hypericin can be used in photodynamic diagnosis as an effective fluorescence marker for tumor detection and visualization. Light-activated hypericin is used as a strong pro-oxidant agent in photodynamic therapy to induce the apoptosis, necrosis, or autophagy of cancer cells due to its high affinity for neoplastic cells [356]. It prevents the uncoating of the HIV by stabilizing its capsid and suppresses the release of reverse transcriptase. Later, endophytic fungi *C. globosum*, *Thielavia subthermophila*, and *Epicoccum nigrum* isolated from *H. perforatum* were also found to produce hypericin [324,326,327].

2.7.2. Pachybasin

Pachybasin (anthraquinone) with antimicrobial and antiviral properties was isolated from *Digitalis lanata* [357]. Later, pachybasin was also isolated from *Phoma sorghina*, an endophyte of *Tithonia diversifolia*, and *Coniothyrium* sp., an endophyte of *Salsola oppositifolia* [316,330].

2.7.3. Pinselin (Cassiollin)

Immunosuppressive and anticancer xanthone pinselin was initially characterized from a strain of *Penicillium amarum*, but later found to be identical to cassiollin reported from *Cassia occidentalis* [336]. Later, plant-derived pinselin was reported from endophytic

Phomopsis sp. isolated from *P. polyphylla* var. *yunnanensis*, *Aspergillus sydowii* isolated from the liverwort *Scapania ciliata*, and *Penicillium* sp. isolated from the leaves of *Sonneratia apetala* [337,338,340].

2.7.4. Plumbagin and Shikonin

Plumbagin and shikonin are anticancer naphthoquinones found in *Plumbago* and *Lithospermum*, respectively. Both can induce in vitro mammalian topoisomerase II-mediated DNA cleavage [358]. The mechanisms underlying the potential antitumor effects of plumbagin involve increased oxidative stress, caspase activity, loss of mitochondrial membrane potential, induction of cytochrome c release, FasL expression, and high Bax levels via activation of the JNK pathway, down-regulation of expression of NF- κ B, suppressed TNF- α -induced phosphorylation of p65 and I κ B kinase (IKK), degradation of I κ B α , and blocking STAT3/ polo-like kinase 1 (PLK1)/AKT signaling [359,360]. Shikonin can induce apoptosis also via ROS generation and the down-regulation of AKT and receptor interacting protein 1 (RIP1)/NF- κ B activity [361]. Both the compounds have also been produced by endophytic fungi, as listed in Table 7.

2.7.5. Rhein

Rheum palmatum is a highly regarded traditional medicinal plant with cathartic, hepatoprotective, nephroprotective, antimicrobial, anti-inflammatory, anticancer, and antiaging properties. The dominant biologically active constituents in the medicinal roots of *Rheum* are anthraquinones rhein, emodin, and physcion. The hepatoprotective activity of rhein is exerted by its lipid lowering, anti-obesity, anti-inflammatory, and anti-oxidant actions. Rhein also suppresses the expression of alpha-smooth muscle actin (α -SMA) and transforming growth factor-beta (TGF- β), which are indicative of decreased hepatic stellate cell and myofibroblast activation [362]. Nephroprotective properties of rhein arise from its anti-inflammatory action along with the suppression of α -SMA, TGF- β , and fibronectin expression. The anti-inflammatory activity of rhein involves inhibition of the NF- κ B pathway, which plays a role in the production of many pro-inflammatory cytokines [363]. The mechanism of rhein anticancer activity involves the inhibition of NF- κ B, MAPK, and PI3K/AKT pathways, eventually regulating cell cycle, angiogenesis, and apoptosis [364,365]. Endophytic *F. solani* from the roots of *R. palmatum* also produced the host-derived compounds rhein and emodin [322].

2.7.6. Tanshinones

Diterpenoid quinone metabolite tanshinones (tanshinone I, tanshinone IIA, tanshinone IIB, isotanshinone I, and cryptotanshinone), found in the roots of *Salvia* spp., are considered to be potent anticancer, antiatherosclerosis, antihypertensive, and neuroprotective agents. Tanshinones' antitumor mechanism involves the inhibition of DNA duplication, cell cycle arrest, regulation of oxidative stress, and reduction of the mitochondrial membrane potential and PTEN-mediated inhibition of the PI3K/AKT pathway to induce apoptosis. Tanshinone I inhibits tumor angiogenesis by the phosphorylation of STAT3 at Tyr705 and hypoxia-induced HIF-1 α accumulation in neoplastic cells. The cardiovascular protective effect of tanshinones is exerted by the inhibition of myocardial apoptosis, cardiac fibrosis, atherosclerosis, oxidized low-density lipoprotein (ox-LDL) uptake, thrombin activation, and thrombosis. Tanshinones exhibit significant neuroprotective effects in various neurodegenerative diseases by selectively suppressing pro-inflammatory gene expression in activated microglia, protecting neurons from the neurotoxicity of A β , and down-regulating the expression of phosphorylated tau [366]. Endophytic fungi *Phoma glomerata* and *Alternaria* sp. residing in the roots of *Salvia miltiorrhiza* produced tanshinones [352,353]. It has also been secreted by endophytic fungi from *Panax* (Table 7). Interestingly, elicitors from the endophytic fungi *T. atroviride* and *C. globosum* promoted the biosynthesis of tanshinones via enhanced expression of related genes in hairy roots of *S. miltiorrhiza* [367,368].

2.8. Miscellaneous Plant-Derived Compounds from Fungal Endophytes

In this section, we grouped diverse classes of compounds such as phenolics, phytoalexins and acids with a total number reaching up to 17 (Table 8).

Table 8. Miscellaneous plant-derived compounds produced by endophytic fungi.

Plant-Derived Compounds	Activities/Applications	Plant Source	Endophytic Source	Host Plant	References
3-Nitropropionic acid (beta-Nitropropionic acid)	Antimycobacterial, nematocidal, succinate dehydrogenase inhibitor	<i>Astragalus falcatus</i> , <i>Coronilla viminalis</i> , <i>Hippocrepis</i> sp., <i>Lotus</i> , <i>Scorpiurus</i> sp., <i>Securigera</i> sp.	<i>Melanconium betulinum</i>	Birches	[369,370]
			<i>Phomopsis phaseoli</i> (syn. <i>Diaporthe phaseolorum</i>)	Rainforest tree	[369]
			<i>Phomopsis</i> spp.	<i>Costus</i> sp.	[370]
			<i>Phomopsis longicolla</i>	<i>Trichilia elegans</i>	[371]
Asarone (Phenyl propane)	Antimicrobial	<i>Cinnamomum camphora</i>	<i>Muscodor tigerii</i>	<i>Cinnamomum camphora</i>	[372]
Azelaic acid (Saturated dicarboxylic acid)	Antimicrobial, anti-inflammatory, anticancer	Wheat, rye, barley	<i>Plectosphaerella cucumerina</i>	<i>Cynanchum auriculatum</i>	[373]
			<i>Aspergillus unguis</i>	<i>Enteromorpha</i> sp.	[374]
Cajanin stilbene acid	Antioxidant, anti-inflammatory, hypoglycemic, neuroprotective	<i>Cajanus cajan</i>	<i>Cytonaema</i> sp.	<i>Quercus</i> sp.	[375]
			<i>Alternaria</i> , <i>Fusarium oxysporum</i> , <i>Fusarium solani</i> , <i>Fusarium proliferatum</i> , <i>Neonectria macrodidym</i>	<i>Cajanus cajan</i>	[376]
Chlorogenic acid (5-O-caffeoylquinic acid) (Cinnamate conjugates)	Antimicrobial, antioxidant, antitumor, immunomodulatory, antiviral	<i>Arnica</i> spp., <i>Arctium lappa</i> , <i>Coffea canephora</i> , <i>Chrysanthemum coronarium</i> , <i>Schefflera heptaphylla</i>	Anonymous	<i>Artemisia indica</i>	[216]
			<i>Sordariomycete</i> sp.	<i>Eucommia ulmoides</i>	[377]
Eugenol (Phenyl propane)	Antimicrobial	<i>Syzygium aromaticum</i>	<i>Alternaria</i> sp.	<i>Rosa damasceana</i>	[378]
			<i>Annulohypoxylon stygium</i>	Anonymous	[379]
			<i>Rhizopus oryzae</i>	<i>Holarrhena pubescens</i>	[380]
			<i>Diaporthe</i> sp., <i>Neopestalotiopsis</i> sp.	<i>Cinnamomum loureiroi</i>	[381]
Digoxin	Cardiac, anticancer	<i>Digitalis lanata</i>	Anonymous	<i>Digitalis lanata</i>	[382]

Table 8. Cont.

Plant-Derived Compounds	Activities/Applications	Plant Source	Endophytic Source	Host Plant	References
Forskolin	Antiglaucoma, anti-HIV, antitumor	<i>Coleus forskohlii</i>	<i>Rhizoctonia bataticola</i>	<i>Coleus forskohlii</i>	[383]
Harpagide (Iridoid glycosides)	Anticancer, anti-inflammatory, Leishmanicidal	<i>Harpagophytum procumbens</i>	<i>Alternaria alternata</i>	<i>Scrophularia ningpoensis</i>	[384,385]
Myrtucommulones (Lactone)	Anticancer, anti-inflammatory	<i>Myrtus communis</i>	<i>Neofusicoccum australe</i> (teleomorph <i>Botryosphaeria australis</i>)	<i>Myrtus communis</i>	[386]
Naphthalene (Aromatic hydrocarbon)	Antibacterial, insect repellent	<i>Ancistrocladus tectorius</i>	<i>Muscodor vitigenus</i>	<i>Paullinia paullinioides</i>	[387,388]
			<i>Nodulisporium</i> sp.	<i>Erica arborea</i>	[389]
			<i>Phoma herbarum</i>	<i>Aegle marmelos</i>	[390]
Panaxynol or Falcarinol or Carotatoxin (Polyacetylene)	Anticancer	<i>Panax ginseng</i> , <i>Falcaria vulgaris</i> , <i>Daucus carota</i> , <i>Hedera</i> spp.	<i>Paecilomyces</i> sp.	<i>Panax ginseng</i>	[295]
Resveratrol (Stilbene polyphenol)	Antioxidant, anticancer, epigenetic modulation	<i>Vitis</i> spp.	<i>Alternaria</i> sp., <i>Aspergillus</i> sp., <i>Botryosphaeria</i> sp., <i>Cephalosporium</i> sp., <i>Geotrichum</i> sp., <i>Mucor</i> sp., <i>Penicillium</i> sp.	<i>Polygonum cuspidatum</i> , <i>Vitis quin-quangularis</i> , <i>Vitis vinifera</i>	[391]
Salidroside, p-tyrosol	Antioxidant, antihypoxic, adaptogenic	<i>Rhodiola rosea</i>	<i>Phialocephala fortinii</i>	<i>Rhodiola</i> sp.	[392]
Salvianolic acid (Polyphenol)	Antioxidant, cardiovascular, cerebrovascular diseases	<i>Salvia miltiorrhiza</i>	<i>Phoma glomerata</i>	<i>Salvia miltiorrhiza</i>	[352]
Tocopherol (Phenol)	Anti-influenza, antioxidant	<i>Ribes</i> sp.	<i>Aspergillus fumigatus</i>	<i>Cynodon dactylon</i>	[393]

2.8.1. Cajaninstilbene Acid (CSA)

The major active constituent of leaves of therapeutic pigeon pea extract is cajaninstilbene acid (CSA), which is a low-molecular weight compound containing two benzene rings joined by a molecule of ethylene. Pharmacological studies have shown that CSA exhibits antioxidant, anti-inflammatory, analgesic, and neuroprotective effects. Its cytoprotective effects against oxidative stress is exhibited by inducing the Nrf2-dependent antioxidant pathway and gene expression of heme oxygenase-1 (HO-1), NAD(P)H quinone oxidoreductase 1 (NQO1), and glutamate–cysteine ligase modifier subunits by activation of PI3K/AKT, ERK, and JNK signaling pathways [394]. The anti-inflammatory activity

of CSA is associated with the inhibition of NF- κ B and MAPK pathways [395]. In a study, CSA attenuated the impairment of learning and memory induced by A β (1–42) oligomers by stimulating A β clearance and inhibiting microglial activation and astrocyte reactivity in the hippocampus. It also decreased the high levels of Glu but increased the low levels of GABA. In addition, CSA inhibited the excessive expression of GluN2B-containing N-methyl-D-aspartate receptors (NMDARs) and up-regulated the downstream protein kinase A (PKA)/CREB/BDNF/tropomyosin receptor kinases (TrkB) signaling pathway. The above findings imply that CSA could be a potential neuroprotective agent at the early stage of Alzheimer's disease [396]. CSA has also been produced by pigeon pea endophytic fungi *Alternaria*, *Fusarium* spp., and *Neonectria macrodidym* [137,376].

2.8.2. Digoxin

The glycoside digoxin from *Digitalis* spp. has been reported to be cardiotoxic and is widely used in the treatment of various heart disorders such as atrial fibrillation, atrial flutter, and heart failure. Digoxin induces an increase in intracellular sodium followed by calcium in the heart by reversibly inhibiting the activity of the myocardial Na⁺-K⁺-ATPase pump, leading to an increased force of myocardial contraction and cardiac output. By stimulating the parasympathetic nerve, it slows electrical conduction in the AV node by increasing the refractory period of cardiac myocytes; therefore, it decreases the ventricular response and heart rate. Overall, the stroke volume is increased while the heart rate is decreased, resulting in a net increase in blood pressure [397]. Crude extracts of fungal cultures isolated from *Digitalis lanata* also showed the production of digoxin [382].

2.8.3. Forskolin (Coleonol)

The roots of Indian Coleus (*Coleus forskohlii*) contain a biologically active labdane diterpene compound forskolin with antiglaucoma, anti-HIV, and antitumor activities. Other approved and potential applications of forskolin range from the treatment of hypertension and heart failure to lipolysis and body weight control [398]. Forskolin activates a variety of adenylate cyclase systems to increase the cellular concentrations of cyclic AMP, which is an important second messenger necessary to elicit cAMP-dependent physiological responses [399]. An endophytic fungus *Rhizoctonia bataticola* isolated from *C. forskohlii* was found to synthesize forskolin [383].

2.8.4. Salidroside and p-Tyrosol (Aglycone of Salidroside)

Rhodiola rosea, a traditional medicinal herb used as stimulant and antidepressant, has great pharmaceutical value including antioxidant, antihypoxic, adaptogenic, cardiovascular, and neuroprotective properties. Its active principals are phenolics (salidroside and p-tyrosol) and glycosides (rosavins) [400]. Salidroside and p-tyrosol inhibit the hypoxia-induced endocytosis of pulmonary Na,K-ATPase via the inhibition of the ROS-AMPK-protein kinase C ζ (PKC ζ) pathway, signifying the use of *Rhodiola* as a popular folk medicine for high-altitude illness [401]. The mechanisms underlying the potential neuroprotective effects of salidroside involve the regulation of oxidative stress response, inflammation, apoptosis, hypothalamus-pituitary-adrenal axis, neurotransmission, neural regeneration, and the cholinergic system [402]. Cui et al. isolated four endophytic fungi from different species of *Rhodiola* that could produce salidroside and p-tyrosol and characterized *P. fortinii* as the most capable and stable producer [392].

3. Avenues and Challenges in Application of Endophyte as Alternative Sources of Plant-Derived Natural Compounds

The success of natural products in drug discovery lies in their enormous structural diversity, diverse pharmacological activities, safety, and inherent binding capacity with other biomolecules [2,9,298]. Reports regarding the biosynthesis of plant-derived natural compounds from endophytic fungi coupled with recent dynamic progress in fermentation, extraction, purification, characterization, and bioassay techniques have enabled us to rapidly characterize valuable novel natural products and access earlier inaccessible en-

dophytic resource [403,404]. Generally, the fermentation process for fungi is short, simple, and economically feasible with a great degree of flexibility for modulation by feeding precursors, elicitors, special enzymes, and modifiers for the efficient enhanced production of bioactive compounds. Endophytes can uniquely biotransform original plant-derived bioactive compounds to their more efficient derivatives, leading to structural and functional diversification [77,136,146]. These studies have evidenced the incredible manipulability of fungal secondary metabolism. There are cases where endophytes up-regulated the synthesis of host compounds and the expression of related genes in the plant host. Hence, each report of the biosynthesis of plant-derived natural compounds from fungal endophytes clearly presents a hopeful way for the efficient and specific production of valuable bioactive natural compounds using endophytes as stable and smart “bio-laboratories”.

However, this approach needs to overcome certain challenges. First, there is an ongoing search for highly productive endophytic fungi for desired plant-derived compounds followed by their strain improvement through epigenetic modulations, mutations, and genetic engineering to make them suitable for industrial applications. Furthermore, we need to elucidate the complete biosynthesis route including all the enzymes and related genes involved through ‘omics’—genomics, transcriptomics, proteomics, and metabolomics—to regulate and manipulate the biosynthesis process for improved productivity [405–407]. Alternatively, the identified biosynthetic pathway of the bioactive compounds can be assembled and mimicked in convenient systems, offering an approach to produce target compounds with ease. Second, we need to know more about the roles of host plant–endophyte interactions, requirements of plant niche, and identities of specific signals/elicitors in the synthesis and induction of host-derived natural compounds by endophytes under the OSMAC strategy to overcome the problem of low yield and attenuation, the major challenges for commercial success of this novel approach [406,408–410]. The reasons for the attenuation of products have been attributed to the lack of apparent signals/molecules arising from host–endophyte and/or endophyte–peer endophytes interactions in axenic monocultures, resulting in the switching off of genes [86]. However, characterization of the specific nature of assumed activator signals/molecules remains to be done. Third, this area needs collaborations between scientists working in this area and in the pharmaceutical industry for the successful industrial scale production of pharmaceutically valuable compound/leads [411]. The pharmaceutical industry must prioritize their endeavors toward the endophyte-dependent biosynthesis of plant-derived natural compounds.

4. Conclusions

After screening a large spectrum of articles dedicated to endophyte research, natural product drug discovery, combinatorial chemistry, genomics, metabolomics ethnobotany, modern medicine, and multidisciplinary science, we curated 101 specific plant-derived medicinal compounds efficiently biosynthesized by hundreds of endophytic fungi. Nonetheless, the exciting progress that has been made in the field of functional genomics, genome mining and genome scanning, fermentation technology, green combinatorial chemistry, and systems biology might remove the roadblocks in the way of commercial success of this innovative approach [282,412,413]. In conclusion, the pursuit of the idea of endophyte-dependent enhanced *in vivo* and *in vitro* production of plant-derived valuable metabolites is of prime importance for the pharmaceutical industries, for the health care systems, and for a “green drug revolution”.

Author Contributions: Conceptualization, A.S., D.K.S. and S.K.G.; Writing—Original Draft Preparation, A.S. and D.K.S.; Writing—Review and Editing, D.K.S., S.K.G., J.F.W. and R.N.K.; Supervision, S.K.G. All authors have read and agreed to the published version of the manuscript.

Funding: This study was supported by CSIR, New Delhi and SERB, New Delhi, India (EEQ/2016/000555 and EEQ/2020/000485). RNK acknowledges funding support from SERB, New Delhi, India (EEQ/2020/000549). J.F.W. was supported by the Rutgers Agricultural Experiment Station and USDA NIFA Multi-State Project W-4147.

Data Availability Statement: Data sharing is not applicable to this article.

Conflicts of Interest: The authors declare no conflict of interest.

References

1. Shen, B. A new golden age of natural products drug discovery. *Cell* **2015**, *163*, 1297–1300. [[CrossRef](#)]
2. Newman, D.J.; Cragg, G.M. Natural products as sources of new drugs from 1981 to 2014. *J. Nat. Prod.* **2016**, *79*, 629–661. [[CrossRef](#)] [[PubMed](#)]
3. Calixto, J.B. The role of natural products in modern drug discovery. *An. Acad. Bras. Cienc.* **2019**, *91*, e20190105. [[CrossRef](#)] [[PubMed](#)]
4. Wilson, B.A.; Thornburg, C.C.; Henrich, C.J.; Grkovic, T.; O’Keefe, B.R. Creating and screening natural product libraries. *Nat. Prod. Rep.* **2020**, *37*, 893–918. [[CrossRef](#)] [[PubMed](#)]
5. Strobel, G. The emergence of endophytic microbes and their biological promise. *J. Fungi* **2018**, *4*, 57. [[CrossRef](#)] [[PubMed](#)]
6. Abdul-Razek, A.S.; El-Nagar, M.E.; Allam, A.; Morsy, O.M.; Othman, S.I. Microbial natural products in drug discovery. *Processes* **2020**, *8*, 470. [[CrossRef](#)]
7. Uzma, F.; Mohan, C.D.; Hashem, A.; Konappa, N.M.; Rangappa, S.; Kamath, P.V.; Singh, B.P.; Mudili, V.; Gupta, V.K.; Siddaiah, C.N.; et al. Endophytic fungi—Alternative sources of cytotoxic compounds: A review. *Front. Pharmacol.* **2018**, *9*, 309. [[CrossRef](#)]
8. Hyde, K.D.; Xu, J.; Rapior, S.; Jeewon, R.; Lumyong, S.; Niego, A.G.T.; Abeywickrama, P.D.; Aluthmuhandiram, J.V.S.; Brahamanage, R.S.; Brooks, S.; et al. The amazing potential of fungi: 50 ways we can exploit fungi industrially. *Fungal Divers.* **2019**, *97*, 1–136. [[CrossRef](#)]
9. Newman, D.J.; Cragg, G.M. Plant endophytes and epiphytes: Burgeoning sources of known and “unknown” cytotoxic and antibiotic agents? *Planta Med.* **2020**, *86*, 1095–1111. [[CrossRef](#)]
10. Christenhusz, M.J.M.; Byng, J.W. The number of known plants species in the world and its annual increase. *Phytotaxa* **2016**, *261*, 201–217. [[CrossRef](#)]
11. Stierle, A.; Strobel, G.; Stierle, D. Taxol and taxane production by *Taxomyces andreanae*, an endophytic fungus of Pacific yew. *Science* **1993**, *260*, 214–216. [[CrossRef](#)] [[PubMed](#)]
12. Aly, A.H.; Debbab, A.; Proksch, P. Fungal endophytes—Secret producers of bioactive plant metabolites. *Pharmazie* **2013**, *68*, 499–505.
13. Nicoletti, R.; Fiorentino, A. Plant bioactive metabolites and drugs produced by endophytic fungi of Spermatophyta. *Agriculture* **2015**, *5*, 918–970. [[CrossRef](#)]
14. Venieraki, A.; Dimou, M.; Katinakis, P. Endophytic fungi residing in medicinal plants have the ability to produce the same or similar pharmacologically active secondary metabolites as their hosts. *Hell. Plant Protect. J.* **2017**, *10*, 51–66. [[CrossRef](#)]
15. Cook, D.; Gardner, D.R.; Pfister, J.A. Swainsonine-containing plants and their relationship to endophytic fungi. *J. Agric. Food Chem.* **2014**, *62*, 7326–7334. [[CrossRef](#)] [[PubMed](#)]
16. Naik, S.; Shaanker, R.U.; Ravikanth, G.; Dayanandan, S. How and why do endophytes produce plant secondary metabolites? *Symbiosis* **2019**, *78*, 193–201. [[CrossRef](#)]
17. Ludwig-Müller, J. Plants and endophytes: Equal partners in secondary metabolite production? *Biotechnol. Lett.* **2015**, *37*, 1325–1334. [[CrossRef](#)] [[PubMed](#)]
18. Knox, R. Introduction to medicinal plants. In *Medicinal Plant Biotechnology*; Knox, R., Ed.; Scientific e-Resources; ED-Tech Press: Essex, UK, 2019; pp. 32–60.
19. Staniek, A.; Bouwmeester, H.; Fraser, P.D.; Kayser, O.; Martens, S.; Tissier, A.; Warzecha, H. Natural products—learning chemistry from plants. *Biotechnol. J.* **2014**, *9*, 326–336. [[CrossRef](#)] [[PubMed](#)]
20. Zeilinger, S.; García-Estrada, C.; Martín, J.F. Fungal secondary metabolites in the “OMICS” Era. In *Biosynthesis and Molecular Genetics of Fungal Secondary Metabolites*; Zeilinger, S., Martín, J.F., García-Estrada, C., Eds.; Springer: New York, NY, USA, 2015; Volume 2, pp. 1–12.
21. Mohanta, T.K. Fungi contain genes associated with flavonoid biosynthesis pathway. *J. Funct. Foods* **2020**, *68*, 103910. [[CrossRef](#)]
22. Esmailzadeh Bahabadi, S.; Sharifi, M.; Behmanesh, M.; Safaie, N.; Murata, J.; Araki, R.; Yamagaki, T.; Satake, H. Time-course changes in fungal elicitor-induced lignan synthesis and expression of the relevant genes in cell cultures of *Linum album*. *J. Plant Physiol.* **2012**, *169*, 487–491. [[CrossRef](#)]
23. Augustin, J.M.; Kuzina, V.; Andersen, S.B.; Bak, S. Molecular activities, biosynthesis and evolution of triterpenoid saponins. *Phytochemistry* **2011**, *72*, 435–457. [[CrossRef](#)] [[PubMed](#)]
24. Feng, P.; Shang, Y.; Cen, K.; Wang, C. Fungal biosynthesis of the bibenzoquinone oosporein to evade insect immunity. *Proc. Nat. Acad. Sci. USA* **2015**, *112*, 11365–11370. [[CrossRef](#)] [[PubMed](#)]
25. Le Pogam, P.; Boustie, J. Xanthonines of lichen source: A 2016 update. *Molecules* **2016**, *21*, 294. [[CrossRef](#)] [[PubMed](#)]
26. Yang, K.; Liang, J.; Li, Q.; Kong, X.; Chen, R.; Jin, Y. *Cladosporium cladosporioides* XJ-AC03, an aconitine-producing endophytic fungus isolated from *Aconitum leucostomum*. *World J. Microbiol. Biotechnol.* **2013**, *29*, 933–938. [[CrossRef](#)]
27. Duan, L.I.; Liwei, G.; Hong, Y. Isolation and identification of producing endophytic fungi of berberine from the plant *Phellodendron amurense*. *J. Anhui. Agric. Sci.* **2009**, *22*, 7.
28. Singh, N.; Sharma, B. Toxicological effects of berberine and sanguinarine. *Front. Mol. Biosci.* **2018**, *5*, 21. [[CrossRef](#)]

29. Vinodhini, D.; Agastian, P. Berberine production by endophytic fungus *Fusarium solani* from *Cosciniium fenestratum*. *Int. J. Biol. Pharm. Res.* **2013**, *4*, 1239–1245.
30. Bhagobaty, R.K.; Joshi, S.R. Metabolite profiling of endophytic fungal isolates of five ethno-pharmacologically important plants of Meghalaya, India. *J. Metab. Syst. Biol.* **2011**, *2*, 20–31.
31. Puri, S.C.; Verma, V.; Amna, T.; Qazi, G.N.; Spiteller, M. An endophytic fungus from *Nothapodytes foetida* that produces camptothecin. *J. Nat. Prod.* **2005**, *68*, 1717–1719. [[CrossRef](#)]
32. Amna, T.; Puri, S.C.; Verma, V.; Sharma, J.P.; Khajuria, R.K.; Musarrat, J.; Spiteller, M.; Qazi, G.N. Bioreactor studies on the endophytic fungus *Entrophospora infrequens* for the production of an anticancer alkaloid camptothecin. *Can. J. Microbiol.* **2006**, *52*, 189–196. [[CrossRef](#)]
33. Rehman, S.; Shawl, A.S.; Verma, V.; Kour, A.; Athar, M.; Andrabi, R.; Sultan, P.; Qazi, G.N. An endophytic *Neurospora* sp. from *Nothapodytes foetida* producing camptothecin. *Prikl. Biokhim. Mikrobiol.* **2008**, *44*, 225–231. [[CrossRef](#)] [[PubMed](#)]
34. Min, C.; Wang, X. Isolation and identification of the 10-hydroxycamptothecin-producing endophytic fungi from *Camptotheca acuminata* Decne. *Acta Bot. Boreal.-Occident. Sin.* **2009**, *29*, 614–617.
35. Rehman, S.; Shawl, A.S.; Kour, A.; Sultan, P.; Ahmad, K.; Khajuria, R.; Qazi, G.N. Comparative studies and identification of camptothecin produced by an endophyte at shake flask and bioreactor. *Nat. Prod. Res.* **2009**, *23*, 1050–1057. [[CrossRef](#)] [[PubMed](#)]
36. Kusari, S.; Zühlke, S.; Spiteller, M. An endophytic fungus from *Camptotheca acuminata* that produces camptothecin and analogues. *J. Nat. Prod.* **2009**, *72*, 2–7. [[CrossRef](#)] [[PubMed](#)]
37. Gurudatt, P.S.; Priti, V.; Shweta, S.; Ramesha, B.T.; Ravikanth, G.; Vasudeva, R.; Amna, T.; Deepika, S.; Ganeshaiyah, K.N.; Shaanker, R.U.; et al. Attenuation of camptothecin production and negative relation between hyphal biomass and camptothecin content in endophytic fungal strains isolated from *Nothapodytes nimmoniana* Graham (Icacinaceae). *Curr. Sci.* **2010**, *98*, 1006–1010.
38. Liu, K.; Ding, X.; Deng, B.; Chen, W. 10-Hydroxycamptothecin produced by a new endophytic *Xylaria* sp., M20, from *Camptotheca acuminata*. *Biotechnol. Lett.* **2010**, *32*, 689–693. [[CrossRef](#)]
39. Shweta, S.; Zuehlke, S.; Ramesha, B.T.; Priti, V.; Kumar, P.M.; Ravikanth, G.; Spiteller, M.; Vasudeva, R.; Shaanker, R.U. Endophytic fungal strains of *Fusarium solani*, from *Apodytes dimidiata* E. Mey. ex Arn (Icacinaceae) produce camptothecin, 10-hydroxycamptothecin and 9 methoxycamptothecin. *Phytochemistry* **2010**, *71*, 117–122. [[CrossRef](#)]
40. Ding, X.; Liu, K.; Deng, B.; Chen, W.; Li, W.; Liu, F. Isolation and characterization of endophytic fungi from *Camptotheca acuminata*. *World J. Microbiol. Biotechnol.* **2013**, *29*, 1831–1838. [[CrossRef](#)]
41. Shweta, S.; Gurumurthy, B.R.; Ravikanth, G.; Ramanan, U.S.; Shivanna, M.B. Endophytic fungi from *Miquelia dentata* Bedd., produce the anti-cancer alkaloid, camptothecine. *Phytomedicine* **2013**, *20*, 337–342. [[CrossRef](#)]
42. Pu, X.; Qu, X.; Chen, F.; Bao, J.; Zhang, G.; Luo, Y. Camptothecin-producing endophytic fungus *Trichoderma atroviride* LY357: Isolation, identification, and fermentation conditions optimization for camptothecin production. *Appl. Microbiol. Biotechnol.* **2013**, *97*, 9365–9375. [[CrossRef](#)]
43. Musavi, S.F.; Dhavale, A.; Balakrishnan, R.M. Optimization and kinetic modeling of cell-associated camptothecin production from an endophytic *Fusarium oxysporum* NFX06. *Prep. Biochem. Biotechnol.* **2015**, *45*, 158–172. [[CrossRef](#)] [[PubMed](#)]
44. Devari, S.; Jaglan, S.; Kumar, M.; Deshidi, R.; Guru, S.; Bhushan, S.; Kushwaha, M.; Gupta, A.P.; Gandhi, S.G.; Sharma, J.P.; et al. Capsaicin production by *Alternaria alternata*, an endophytic fungus from *Capsicum annum*; LC–ESI–MS/MS analysis. *Phytochemistry* **2014**, *98*, 183–189. [[CrossRef](#)] [[PubMed](#)]
45. Hu, X.; Li, W.; Yuan, M.; Li, C.; Liu, S.; Jiang, C.; Wu, Y.; Cai, K.; Liu, Y. Homoharringtonine production by endophytic fungus isolated from *Cephalotaxus hainanensis* Li. *World J. Microbiol. Biotechnol.* **2016**, *32*, 110. [[CrossRef](#)] [[PubMed](#)]
46. Li, W.K.; Zhou, J.Y.; Lin, Z.W.; Hu, Z. Study on fermentation condition for production of Huperzine A from endophytic fungus 2F09P03B of *Huperzia serrata*. *Chin. J. Med. Chem.* **2007**, *2*, 254–259.
47. Ju, Z.; Wang, J.; Pan, S.L. Isolation and preliminary identification of the endophytic fungi which produce Hupzine A from four species in Hupziaceae and determination of Huperzine A by HPLC. *J. Med. Sci.* **2009**, *36*, 445–449.
48. Zhou, S.L.; Yang, F.; Lan, S.L.; Xu, N.; Hong, Y.H. Huperzine A producing conditions from endophytic fungus in SHB *Huperzia serrata*. *J. Microbiol.* **2009**, *3*, 32–36.
49. Zhu, D.; Wang, J.; Zeng, Q.; Zhang, Z.; Yan, R. A novel endophytic Huperzine A–producing fungus, *Shiraia* sp. Slf14, isolated from *Huperzia serrata*. *J. Appl. Microbiol.* **2010**, *109*, 1469–1478. [[CrossRef](#)]
50. Zhang, Z.B.; Zeng, Q.G.; Yan, R.M.; Wang, Y.; Zou, Z.R.; Zhu, D. Endophytic fungus *Cladosporium cladosporioides* LF70 from *Huperzia serrata* produces Huperzine A. *World J. Microbiol. Biotechnol.* **2011**, *27*, 479–486. [[CrossRef](#)]
51. Dong, L.H.; Fan, S.W.; Ling, Q.Z.; Huang, B.B.; Wei, Z.J. Identification of Huperzine A-producing endophytic fungi isolated from *Huperzia serrata*. *World J. Microbiol. Biotechnol.* **2014**, *30*, 1011–1017. [[CrossRef](#)]
52. Su, J.; Yang, M. Huperzine A production by *Paecilomyces tenuis* YS-13, an endophytic fungus isolated from *Huperzia serrata*. *Nat. Prod. Res.* **2015**, *29*, 1035–1041. [[CrossRef](#)]
53. Su, J.; Liu, H.; Guo, K.; Chen, L.; Yang, M.; Chen, Q. Research advances and detection methodologies for microbe-derived acetylcholinesterase inhibitors: A systemic review. *Molecules* **2017**, *22*, 176. [[CrossRef](#)] [[PubMed](#)]
54. Le, T.T.M.; Hoang, A.T.H.; Le, T.T.; Vo, T.T.B.; Van Quyen, D.; Chu, H.H. Isolation of endophytic fungi and screening of Huperzine A–producing fungus from *Huperzia serrata* in Vietnam. *Sci. Rep.* **2019**, *9*, 1–3.
55. Cruz-Miranda, O.L.; Folch-Mallol, J.; Martínez-Morales, F.; Gesto-Borroto, R.; Villarreal, M.L.; Taketa, A.C. Identification of a Huperzine A-producing endophytic fungus from *Phlegmariurus taxifolius*. *Mol. Biol. Rep.* **2020**, *47*, 489–495. [[CrossRef](#)] [[PubMed](#)]

56. Le, T.T.M.; Hoang, A.T.H.; Nguyen, N.P.; Le, T.T.B.; Trinh, H.T.T.; Vo, T.T.B.; Van Quyen, D. A novel huperzine A-producing endophytic fungus *Fusarium* sp. Rsp5.2 isolated from *Huperzia serrata*. *Biotechnol. Lett.* **2020**, *42*, 1–9. [[CrossRef](#)] [[PubMed](#)]
57. Wang, D.; Zhu, J.; Wang, S.; Wang, X.; Ou, Y.; Wei, D.; Xueping, L. Antitussive, expectorant and anti-inflammatory alkaloids from *Bulbus Fritillariae cirrhosae*. *Fitoterapia* **2011**, *82*, 1290–1294. [[CrossRef](#)]
58. Pan, F.; Hou, K.; Gao, F.; Hu, B.; Chen, Q.; Wu, W. Peimisine and peiminine production by endophytic fungus *Fusarium* sp. isolated from *Fritillaria unibracteata* var. *wabensis*. *Phytomedicine* **2014**, *21*, 1104–1109. [[CrossRef](#)]
59. Pan, F.; Su, X.; Hu, B.; Yang, N.; Chen, Q.; Wu, W. *Fusarium redolens* 6WBY3, an endophytic fungus isolated from *Fritillaria unibracteata* var. *wabuensis*, produces peimisine and imperialine-3 β -d-glucoside. *Fitoterapia* **2015**, *103*, 213–221. [[CrossRef](#)]
60. Verma, V.C.; Lobkovsky, E.; Gange, A.C.; Singh, S.K.; Prakash, S. Piperine production by endophytic fungus *Periconia* sp. isolated from *Piper longum* L. *J. Antibiot.* **2011**, *64*, 427–431. [[CrossRef](#)]
61. Chithra, S.; Jasim, B.; Sachidanandan, P.; Jyothis, M.; Radhakrishnan, E.K. Piperine production by endophytic fungus *Colletotrichum gloeosporioides* isolated from *Piper nigrum*. *Phytomedicine* **2014**, *21*, 534–540. [[CrossRef](#)]
62. Chithra, S.; Jasim, B.; Anisha, C.; Mathew, J.; Radhakrishnan, E.K. LC-MS/MS based identification of piperine production by endophytic *Mycosphaerella* sp. PF13 from *Piper nigrum*. *Appl. Biochem. Biotechnol.* **2014**, *173*, 30–35. [[CrossRef](#)]
63. Chithra, S.; Jasim, B.; Mathew, J.; Radhakrishnan, E.K. Endophytic *Phomopsis* sp. colonization in *Oryza sativa* was found to result in plant growth promotion and piperine production. *Physiol. Planta* **2017**, *160*, 437–446.
64. Maehara, S.; Simanjuntak, P.; Maetani, Y.; Kitamura, C.; Ohashi, K.; Shibuya, H. Ability of endophytic filamentous fungi associated with *Cinchona ledgeriana* to produce *Cinchona* alkaloids. *J. Nat. Med.* **2013**, *67*, 421–423. [[CrossRef](#)] [[PubMed](#)]
65. Hidayat, I.; Radiastuti, N.; Rahayu, G.; Achmadi, S.; Okane, I. Three quinine and cinchonidine producing *Fusarium* species from Indonesia. *Curr. Res. Environ. Appl. Microbiol.* **2016**, *6*, 20–34. [[CrossRef](#)]
66. Kumara, P.M.; Zuehlke, S.; Priti, V.; Ramesha, B.T.; Shweta, S.; Ravikanth, G.; Vasudeva, R.; Santhoshkumar, T.R.; Spittler, M.; Uma Shaanker, R. *Fusarium proliferatum*, an endophytic fungus from *Dysoxylum binectariferum* Hook.f, produces rohitukine, a chromane alkaloid possessing anti-cancer activity. *Antonie Van Leeuwenhoek* **2012**, *101*, 323–329. [[CrossRef](#)] [[PubMed](#)]
67. Kumara, P.M.; Soujanya, K.N.; Ravikanth, G.; Vasudeva, R.; Ganeshaiyah, K.N.; Shaanker, R.U. Rohitukine, a chromone alkaloid and a precursor of flavopiridol, is produced by endophytic fungi isolated from *Dysoxylum binectariferum* Hook.f and *Amoora rohituka* (Roxb). Wight & Arn. *Phytomedicine* **2014**, *21*, 541–546.
68. Wang, X.J.; Min, C.L.; Ge, M.; Zuo, R.H. An endophytic sanguinarine-producing fungus from *Macleaya cordata*, *Fusarium proliferatum* BLH51. *Curr. Microbiol.* **2014**, *68*, 336–341. [[CrossRef](#)]
69. Yin, H.; Chen, J.L. Sipeimine-producing endophytic fungus isolated from *Fritillaria ussuriensis*. *Z. Naturforsch.* **2008**, *63*, 789. [[CrossRef](#)]
70. El-Hawary, S.; Mohammed, R.; AbouZid, S.; Bakeer, W.; Ebel, R.; Sayed, A.; Rateb, M. Solamargine production by a fungal endophyte of *Solanum nigrum*. *J. Appl. Microbiol.* **2016**, *120*, 900–911. [[CrossRef](#)]
71. Ralphs, M.H.; Creamer, R.; Baucom, D.; Gardner, D.R.; Welsh, S.L.; Graham, J.D.; Hart, C.; Cook, D.; Stegelmeier, B.L. Relationship between the endophyte *Embellisia* spp. and the toxic alkaloid swainsonine in major locoweed species (*Astragalus* and *Oxytropis*). *J. Chem. Ecol.* **2008**, *34*, 32–38. [[CrossRef](#)]
72. Baucom, D.L.; Romero, M.; Belfon, R.; Creamer, R. Two new species of *Undifilum*, fungal endophytes of *Astragalus* (locoweeds) in the United States. *Botany* **2012**, *90*, 866–875. [[CrossRef](#)]
73. Lu, H.; Chen, J.; Lu, W.; Ma, Y.; Zhao, B.; Wang, J. Isolation and identification of swainsonine-producing fungi found in locoweeds and their rhizosphere soil. *Afr. J. Microbiol. Res.* **2012**, *6*, 4959–4969.
74. Grum, D.S.; Cook, D.; Baucom, D.; Mott, I.W.; Gardner, D.R.; Creamer, R.; Allen, J.G. Production of the alkaloid swainsonine by a fungal endophyte in the host *Swainsona canescens*. *J. Nat. Prod.* **2013**, *76*, 1984–1988. [[CrossRef](#)] [[PubMed](#)]
75. Guo, B.; Li, H.; Zhang, L. Isolation of an fungus producingvinbrastine. *J. Yunnan Univ. (Nat. Sci.)* **1998**, *20*, 214–215.
76. Zhang, L.; Guo, B.; Li, H.; Zeng, S.; Shao, H.; Gu, S.; Wei, R. Preliminary study on the isolation of endophytic fungus of *Catharanthus roseus* and its fermentation to produce products of therapeutic value. *Chin. Tradit. Herb. Drugs* **2000**, *31*, 805–807.
77. Kumar, A.; Patil, D.; Rajamohanam, P.R.; Ahmad, A. Isolation, purification and characterization of vinblastine and vincristine from endophytic fungus *Fusarium oxysporum* isolated from *Catharanthus roseus*. *PLoS ONE* **2013**, *8*, e71805. [[CrossRef](#)]
78. Palem, P.P.; Kuriakose, G.C.; Jayabaskaran, C. An endophytic fungus, *Talaromyces radicus*, isolated from *Catharanthus roseus*, produces vincristine and vinblastine, which induce apoptotic cell death. *PLoS ONE* **2015**, *10*, 12. [[CrossRef](#)] [[PubMed](#)]
79. Kuriakose, G.C.; Palem, P.P.; Jayabaskaran, C. Fungal vincristine from *Eutypella* spp-CrP14 isolated from *Catharanthus roseus* induces apoptosis in human squamous carcinoma cell line-A431. *BMC Complement. Alternat. Med.* **2016**, *16*, 302. [[CrossRef](#)]
80. Na, R.; Jiajia, L.; Dongliang, Y.; Yingzi, P.; Juan, H.; Xiong, L.; Nana, Z.; Jing, Z.; Yitian, L. Identification of vincamine indole alkaloids producing endophytic fungi isolated from *Nerium indicum*, Apocynaceae. *Microbiol. Res.* **2016**, *192*, 114–121. [[CrossRef](#)] [[PubMed](#)]
81. Yin, H.; Sun, Y.H. Vincamine-producing endophytic fungus isolated from *Vinca minor*. *Phytomedicine* **2011**, *18*, 802–805. [[CrossRef](#)] [[PubMed](#)]
82. Anadón, A.; Martínez-Larrañaga, M.R.; Ares, I.; Martínez, M.A. Interactions between nutraceuticals/nutrients and therapeutic drugs. In *Nutraceuticals*; Gupta, R.C., Ed.; Academic Press: Cambridge, MA, USA, 2016; pp. 855–874.
83. Yin, J.; Ye, J.; Jia, W. Effects and mechanisms of berberine in diabetes treatment. *Acta Pharma. Sin. B* **2012**, *2*, 327–334. [[CrossRef](#)]
84. Wall, M.E.; Wani, M.C. Camptothecin and taxol: From discovery to clinic. *J. Ethnopharmacol.* **1996**, *51*, 239–254. [[CrossRef](#)]

85. Kai, G.; Wu, C.; Gen, L.; Zhang, L.; Cui, L.; Ni, X. Biosynthesis and biotechnological production of anti-cancer drug Camptothecin. *Phytochem. Rev.* **2015**, *14*, 525–539. [[CrossRef](#)]
86. Bhalkar, B.N.; Patil, S.M.; Govindwar, S.P. Camptothecine production by mixed fermentation of two endophytic fungi from *Nothapodytes nimmoniana*. *Fungal Biol.* **2016**, *120*, 873–883. [[CrossRef](#)] [[PubMed](#)]
87. Srinivasan, K. Biological activities of red pepper (*Capsicum annuum*) and its pungent principle capsaicin: A review. *Crit. Rev. Food Sci. Nutr.* **2016**, *56*, 1488–1500. [[CrossRef](#)] [[PubMed](#)]
88. Fattori, V.; Hohmann, M.S.; Rossaneis, A.C.; Pinho-Ribeiro, F.A.; Verri, W.A. Capsaicin: Current understanding of its mechanisms and therapy of pain and other pre-clinical and clinical uses. *Molecules* **2016**, *21*, 844. [[CrossRef](#)]
89. Perdue, R.E., Jr.; Spetzman, L.A.; Rowell, R.G. *Cephalotaxus*-source of harringtonine, a promising new anti-cancer alkaloid. *Am. Horticult. Soc.* **1970**, *49*, 19–22.
90. Kantarjian, H.M.; O'Brien, S.; Cortes, J. Homoharringtonine/omacetaxine mepesuccinate: The long and winding road to Food and Drug Administration approval. *Clin. Lymphoma Myeloma Leuk.* **2013**, *13*, 530–533. [[CrossRef](#)]
91. Wang, Y.; Lai, Z.; Li, X.X.; Yan, R.M.; Zhang, Z.B.; Yang, H.L.; Zhu, D. Isolation, diversity and acetylcholinesterase inhibitory activity of the culturable endophytic fungi harboured in *Huperzia serrata* from Jinggang Mountain, China. *World J. Microbiol. Biotechnol.* **2016**, *32*, 20. [[CrossRef](#)]
92. Stojanović-Radić, Z.; Pejčić, M.; Dimitrijević, M.; Aleksić, A.; Anil Kumar, N.V.; Salehi, B.; Cho, W.C.; Sharifi-Rad, J. Piperine-A Major Principle of Black Pepper: A review of its bioactivity and studies. *Appl. Sci.* **2019**, *9*, 4270. [[CrossRef](#)]
93. Achan, J.; Talisuna, A.O.; Erhart, A.; Yeka, A.; Tibenderana, J.K.; Baliraine, F.N.; Rosenthal, P.J.; D'Alessandro, U. Quinine, an old anti-malarial drug in a modern world: Role in the treatment of malaria. *Malar. J.* **2011**, *10*, 144. [[CrossRef](#)]
94. Simanjuntak, P.; Parwati, T.; Bustanussalam; Prana, T.K.; Wibowo, S.; Shibuya, H. Isolasi dan kultivasimikrobaedofitpenghasilsenyawa alkaloid kinkonadariCinchona spp. *J. Mikrobiol. Indones.* **2002**, *7*, 27–30.
95. Kamil, M.; Jadiya, P.; Sheikh, S.; Haque, E.; Nazir, A.; Lakshmi, V.; Mir, S.S. The chromone alkaloid, rohitukine, affords anti-cancer activity via modulating apoptosis pathways in A549 cell line and yeast mitogen activated protein kinase (MAPK) pathway. *PLoS ONE* **2015**, *10*, e0137991.
96. Park, S.Y.; Jin, M.L.; Kim, Y.H.; Lee, S.J.; Park, G. Sanguinarine inhibits invasiveness and the MMP-9 and COX-2 expression in TPA-induced breast cancer cells by inducing HO-1 expression. *Oncol. Rep.* **2014**, *31*, 497–504. [[CrossRef](#)] [[PubMed](#)]
97. Jain, R.; Sharma, A.; Gupta, S.; Sarethy, I.P.; Gabrani, R. *Solanum nigrum*: Current perspectives on therapeutic properties. *Altern. Med. Rev.* **2011**, *16*, 78–85. [[PubMed](#)]
98. Liu, L.F.; Liang, C.H.; Shiu, L.Y.; Lin, W.L.; Lin, C.C.; Kuo, K.W. Action of solamargine on human lung cancer cells—enhancement of the susceptibility of cancer cells to TNFs. *FEBS Lett.* **2004**, *577*, 67–74. [[CrossRef](#)] [[PubMed](#)]
99. Oldrup, E.; McLain-Romero, J.; Padilla, A.; Moya, A.; Gardner, D.; Creamer, R. Localization of endophytic *Undifilum* fungi in locoweed seed and influence of environmental parameters on a locoweed in vitro culture system. *Botany* **2010**, *88*, 512–521. [[CrossRef](#)]
100. Moudi, M.; Go, R.; Yien, C.Y.S.; Nazre, M. Vinca alkaloids. *Int. J. Prevent. Med.* **2013**, *4*, 1231.
101. Vora, S.C.; Gujar, K.N. Vinpocetine: Hype, hope and hurdles towards neuroprotection. *Asian J. Pharma. Res. Develop.* **2013**, *1*, 17–23.
102. Matos, M.J.; Santana, L.; Uriarte, E.; Abreu, O.A.; Molina, E.; Yordi, E.G. Coumarins—An important class of phytochemicals. *Phytochem. Isol. Characterisation Role Hum. Health* **2015**, *30*, 113–140.
103. Huang, Z.; Yang, J.; Cai, X.; She, Z.; Lin, Y. A new furanocoumarin from the mangrove endophytic fungus *Penicillium* sp. (ZH16). *Nat. Prod. Res.* **2012**, *26*, 1291–1295. [[CrossRef](#)]
104. Zaher, A.M.; Moharram, A.M.; Davis, R.; Panizzi, P.; Makboul, M.A.; Calderón, A.I. Characterisation of the metabolites of an antibacterial endophyte *Botryodiplodiatheobromae* Pat. of *Dracaena draco* L. by LC–MS/MS. *Nat. Prod. Res.* **2015**, *29*, 2275–2281. [[CrossRef](#)] [[PubMed](#)]
105. Yamazaki, T.; Tokiwa, T. Isofraxidin, a coumarin component from *Acanthopanax senticosus*, inhibits matrix metalloproteinase-7 expression and cell invasion of human hepatoma cells. *Biol. Pharma. Bull.* **2010**, *33*, 1716–1722. [[CrossRef](#)] [[PubMed](#)]
106. Cheng, M.J.; Wu, M.D.; Hsieh, S.Y.; Su, Y.S.; Chen, I.S.; Yuan, G.F. Secondary metabolites from the endophytic fungus *Annulohyphomyces boveri* var. *microspora* BCRC 34012. *Chem. Nat. Comp.* **2011**, *47*, 536–540. [[CrossRef](#)]
107. Huang, Z.; Yang, J.; She, Z.; Lin, Y. Isoflavones from the mangrove endophytic fungus *Fusarium* sp. (ZZF41). *Nat. Prod. Commun.* **2010**, *5*, 1771–1773. [[CrossRef](#)]
108. Findlay, J.A.; Buthelezi, S.; Lavoie, R.; Peña-Rodríguez, L.; Miller, J.D. Bioactive isocoumarins and related metabolites from conifer endophytes. *J. Nat. Prod.* **1995**, *58*, 1759–1766. [[CrossRef](#)] [[PubMed](#)]
109. Schmeda-Hirschmann, G.; Hormazabal, E.; Astudillo, L.; Rodríguez, J.; Theoduloz, C. Secondary metabolites from endophytic fungi isolated from the Chilean gymnosperm *Prumnopitys andina* (Lleuque). *World J. Microbiol. Biotechnol.* **2005**, *21*, 27–32. [[CrossRef](#)]
110. Pongcharoen, W.; Rukachaisirikul, V.; Phongpaichit, S.; Sakayaroj, J. A new dihydrobenzofuran derivative from the endophytic fungus *Botryosphaeria mamane* PSU-M76. *Chem. Pharm. Bull.* **2007**, *55*, 1404–1405. [[CrossRef](#)]
111. Amaral, L.S.; Murgu, M.; Rodrigues-Fo, E.; de Souza, A.Q.; de Moura Sarquis, M.I. A saponin tolerant and glycoside producer xylariaceous fungus isolated from fruits of *Sapindus saponaria*. *World J. Microbiol. Biotechnol.* **2008**, *24*, 1341–1348. [[CrossRef](#)]

112. de Oliveira, C.M.; Regasini, L.O.; Silva, G.H.; Pfenning, L.H.; Young, M.C.M.; Berlinck, R.G.S.; Bolzani, V.S.; Araujo, A.R. Dihydroisocoumarins produced by *Xylaria* sp. and *Penicillium* sp., endophytic fungi associated with *Piper aduncum* and *Alibertia macrophylla*. *Phytochem. Lett.* **2011**, *4*, 93–96. [[CrossRef](#)]
113. Cheng, M.J.; Wu, M.D.; Yuan, G.F.; Chen, Y.L.; Su, Y.S.; Hsieh, M.T.; Chen, I.S. Secondary metabolites and cytotoxic activities from the endophytic fungus *Annulohypoxylonsquamulosum*. *Phytochem. Lett.* **2012**, *5*, 219–223. [[CrossRef](#)]
114. Zhao, J.H.; Zhang, Y.L.; Wang, L.W.; Wang, J.Y.; Zhang, C.L. Bioactive secondary metabolites from *Nigrospora* sp. LLGLM003, an endophytic fungus of the medicinal plant *Moringa oleifera* Lam. *World J. Microbiol. Biotechnol.* **2012**, *28*, 2107–2112. [[CrossRef](#)] [[PubMed](#)]
115. Ramos, H.P.; Simão, M.R.; de Souza, J.M.; Magalhães, L.G.; Rodrigues, V.; Ambrósio, S.R.; Said, S. Evaluation of dihydroisocoumarins produced by the endophytic fungus *Arthrimum* state of *Apiosporamontagnei* against *Schistosoma mansoni*. *Nat. Prod. Res.* **2013**, *27*, 2240–2243. [[CrossRef](#)] [[PubMed](#)]
116. Rukachaisirikul, V.; Buadam, S.; Sukpondma, Y.; Phongpaichit, S.; Sakayaroj, J.; Hutadilok-Towatanad, N. Indanone and mellein derivatives from the *Garcinia*-derived fungus *Xylaria* sp. PSU-G12. *Phytochem. Lett.* **2013**, *6*, 135–138. [[CrossRef](#)]
117. Wang, J.; Wang, G.; Zhang, Y.; Zheng, B.; Zhang, C.; Wang, L. Isolation and identification of an endophytic fungus *Pezizula* sp. in *Forsythia viridissima* and its secondary metabolites. *World J. Microbiol. Biotechnol.* **2014**, *30*, 2639–2644. [[CrossRef](#)] [[PubMed](#)]
118. Fan, N.W.; Chang, H.S.; Cheng, M.J.; Hsieh, S.Y.; Liu, T.W.; Yuan, G.F.; Chen, I.S. Secondary metabolites from the endophytic fungus *Xylaria cubensis*. *Helv. Chim. Acta* **2014**, *97*, 1689–1699. [[CrossRef](#)]
119. Seida, A.A.A.; Kinghorn, D.; Cordell, G.A.; Farnsworth, N.A. Isolation of bergapten and marmesin from *Balanites aegyptiaca*. *Planta Med.* **1981**, *43*, 92–103. [[CrossRef](#)]
120. Xie, Y.; Huang, X.; Hu, S.Y.; Qiu, X.J.; Zhang, Y.J.; Ren, P.; Wang, Y.; Ji, H.; Zhang, C.H.; Xie, W.B.; et al. Meranzin hydrate exhibits anti-depressive and prokinetic-like effects through regulation of the shared alpha 2-adrenoceptor in the brain–gut axis of rats in the forced swimming test. *Neuropharmacology* **2013**, *67*, 318–325. [[CrossRef](#)]
121. Chebrolua, K.K.; Jayaprakash, G.K.; Jifon, J.; Patil, B.S. Purification of coumarins, including meranzin and pranferin, from grapefruit by solvent partitioning and a hyphenated chromatography. *Separat. Purif. Technol.* **2013**, *116*, 137–144. [[CrossRef](#)]
122. Li, J.; Li, X.; Li, Z.; Zhang, L.; Liu, Y.; Ding, H.; Yin, S. Isofraxidin, a coumarin component improves high-fat diet induced hepatic lipid homeostasis disorder and macrophage inflammation in mice. *Food Funct.* **2017**, *8*, 2886–2896. [[CrossRef](#)]
123. Yim, S.H.; Tabassum, N.; Kim, W.H.; Cho, H.; Lee, J.H.; Batkhuu, G.J.; Kim, H.J.; Oh, W.K.; Jung, D.W.; Williams, D.R. Isolation and characterization of isofraxidin 7-O-(6'-Op-Coumaroyl)- β -glucopyranoside from *Artemisia capillaris* Thunberg: A novel, nontoxic hyperpigmentation agent that is effective in vivo. *Evid. Based Complement. Alternat. Med.* **2017**, *2017*, 1–12. [[CrossRef](#)]
124. Majnooni, M.B.; Fakhri, S.; Shokoohinia, Y.; Mojarab, M.; Kazemi-Afrakoti, S.; Farzaei, M.H. Isofraxidin: Synthesis, biosynthesis, isolation, pharmacokinetic and pharmacological properties. *Molecules* **2020**, *25*, 2040. [[CrossRef](#)] [[PubMed](#)]
125. Abu-mustafam, E.A.; Fayez, B.E. Natural Coumarins. I. marmesin and marmesinin, further products from the fruits of *Ammi majus* L. *J. Org. Chem.* **1961**, *26*, 161–166. [[CrossRef](#)]
126. Nishikawa, E. Biochemistry of filamentous fungi. II. A metabolic product of *Aspergillus melleus* Yukawa. Part I. *Bull. Agric. Chem. Soc. Jpn.* **1933**, *9*, 107–109.
127. Das, A.J. *Moringa oleifera* (Lamm.): A plant with immense importance. *J. Biol. Act. Prod. Nat.* **2012**, *2*, 307–315. [[CrossRef](#)]
128. Chacón-Morales, P.; Amaro-Luis, J.M.; Bahsas, A. Isolation and characterization of (+)-mellein, the first isocoumarin reported in *Stevia* genus. *Avan. Quím.* **2013**, *8*, 145–151.
129. Hornick, A.; Lieb, A.; Vo, N.P.; Rollinger, J.M.; Stuppner, H.; Prast, H. The coumarin scopoletin potentiates acetylcholine release from synaptosomes, amplifies hippocampal long-term potentiation and ameliorates anticholinergic-and age-impaired memory. *Neuroscience* **2011**, *197*, 280–292. [[CrossRef](#)]
130. Liu, X.L.; Zhang, L.; Fu, X.L.; Chen, K.; Qian, B.C. Effect of scopoletin on PC3 cell proliferation and apoptosis. *Acta Pharmacol. Sin.* **2001**, *22*, 929–933.
131. Yu, S.M.; Hu, D.H.; Zhang, J.J. Umbelliferone exhibits anticancer activity via the induction of apoptosis and cell cycle arrest in HepG2 hepatocellular carcinoma cells. *Mol. Med. Rep.* **2015**, *12*, 3869–3873. [[CrossRef](#)]
132. Shukla, S.; Gupta, S. Apigenin: A promising molecule for cancer prevention. *Pharm. Res.* **2010**, *27*, 962–978. [[CrossRef](#)]
133. Panda, S.; Kar, A. Apigenin (4', 5, 7-trihydroxyflavone) regulates hyperglycaemia, thyroid dysfunction and lipid peroxidation in alloxan-induced diabetic mice. *J. Pharm. Pharmacol.* **2007**, *59*, 1543–1548. [[CrossRef](#)]
134. Zhou, S.L.; Zhou, S.L.; Wang, M.X.; Chen, S.L. Two compounds from the endophytic *Colletotrichum* sp. of *Ginkgo biloba*. *Nat. Prod. Comm.* **2011**, *6*, 1131–1132. [[CrossRef](#)]
135. Gao, Y.; Zhao, J.; Zu, Y.; Fu, Y.; Liang, L.; Luo, M.; Wang, W.; Efferth, T. Antioxidant properties, superoxide dismutase and glutathione reductase activities in HepG2 cells with a fungal endophyte producing apigenin from pigeon pea [*Cajanus cajan* (L.) Millsp.]. *Food Res. Int.* **2012**, *49*, 147–152. [[CrossRef](#)]
136. Tian, Y.; Amand, S.; Buisson, D.; Kunz, C.; Hachette, F.; Dupont, J.; Nay, B.; Prado, S. The fungal leaf endophyte *Paraconiothyrium variabile* specifically metabolizes the host-plant metabolome for its own benefit. *Phytochemistry* **2014**, *108*, 95–101. [[CrossRef](#)] [[PubMed](#)]
137. Zhao, J.; Li, C.; Wang, W.; Zhao, C.; Luo, M.; Mu, F.; Fu, Y.; Zu, Y.; Yao, M. *Hypocrea lixii*, novel endophytic fungi producing anticancer agent cajanol, isolated from pigeon pea (*Cajanus cajan* [L.] Millsp.). *J. Appl. Microbiol.* **2013**, *115*, 102–113. [[CrossRef](#)] [[PubMed](#)]

138. Wang, J.; Yao, L.Y.; Lu, Y.H. *Ceriporialacerata* DMC1106, a new endophytic fungus: Isolation, identification, and optimal medium for 2',4'-dihydroxy-6'-methoxy-3',5'-dimethylchalcone production. *Biotechnol. Bioprocess Eng.* **2013**, *18*, 669–678. [[CrossRef](#)]
139. Seetharaman, P.; Gnanasekar, S.; Chandrasekaran, R.; Chandrakasan, G.; Kadarkarai, M.; Sivaperumal, S. Isolation and characterization of anticancer flavone chrysin (5,7-dihydroxy flavone)-producing endophytic fungi from *Passiflora incarnata* L. leaves. *Ann. Microbiol.* **2017**, *67*, 321–331. [[CrossRef](#)]
140. Wang, Y.; Xu, L.; Ren, W.; Zhao, D.; Zhu, Y.; Wu, X. Bioactive metabolites from *Chaetomium globosum* L18, an endophytic fungus in the medicinal plant *Curcuma wenyujin*. *Phytomedicine* **2012**, *19*, 364–368. [[CrossRef](#)]
141. Yan, J.; Qi, N.; Wang, S.; Gadhav, K.; Yang, S. Characterization of secondary metabolites of an endophytic fungus from *Curcuma wenyujin*. *Curr. Microbiol.* **2014**, *69*, 740–744. [[CrossRef](#)]
142. Chaturvedi, P.; Gajbhiye, S.; Roy, S.; Dudhale, R.; Chowdhary, A. Determination of Kaempferol in extracts of *Fusarium chlamydosporum*, an endophytic fungi of *Tylophora indica* (Asclepeadaceae) and its anti-microbial activity. *J. Pharm. Biol. Sci.* **2014**, *9*, 51–55.
143. Huang, J.X.; Zhang, J.; Zhang, X.R.; Zhang, K.; Zhang, X.; He, X.R. *Mucor fragilis* as a novel source of the key pharmaceutical agents podophyllotoxin and kaempferol. *Pharm. Biol.* **2014**, *52*, 1237–1243. [[CrossRef](#)]
144. Zhao, J.; Ma, D.; Luo, M.; Wang, W.; Zhao, C.; Zu, Y.; Fu, Y.; Wink, M. In vitro antioxidant activities and antioxidant enzyme activities in HepG2 cells and main active compounds of endophytic fungus from pigeon pea [*Cajanus cajan* (L.) Millsp.]. *Food Res. Int.* **2014**, *56*, 243–251. [[CrossRef](#)]
145. Qiu, M.; Xie, R.; Shi, Y.; Zhang, H.; Chen, H. Isolation and identification of two flavonoid-producing endophytic fungi from *Ginkgo biloba* L. *Ann. Microbiol.* **2010**, *60*, 143–150. [[CrossRef](#)]
146. Ebada, S.S.; Eze, P.; Okoye, F.B.; Esimone, C.O.; Proksch, P. The fungal endophyte *Nigrosporaoryzae* produces quercetin monoglycosides previously known only from plants. *ChemistrySelect* **2016**, *16*, 2767–2771. [[CrossRef](#)]
147. Hu, M.Y.; Zhong, G.H.; Sun, Z.T.; Sh, G.; Liu, H.M.; Liu, X.Q. Insecticidal activities of secondary metabolites of endophytic *Penicillium* sp. in *Derris elliptica* Benth. *J. Appl. Entomol.* **2005**, *129*, 413–417. [[CrossRef](#)]
148. Fan, Y.F.; Zhan, S.F.; Chen, Y.; Gan, J.L.; Peng, Q.; Liu, Z.J.; Li, S.J. Study on endophytic fungi of *Pteris multifida* II: A preliminary study on a strain of Rutin-producing endophytic fungi. *J. Fung. Res.* **2007**, *4*, 008.
149. Huang, W.; Cai, Y.; Hyde, K.D.; Corke, H.; Sun, M. Endophytic fungi from *Nerium oleander* L (Apocynaceae): Main constituents and antioxidant activity. *World J. Microbiol. Biotechnol.* **2007**, *23*, 1253–1263. [[CrossRef](#)]
150. Liu, X.; Dong, M.; Chen, X.; Jiang, M.; Lv, X.; Yan, G. Antioxidant activity and phenolics of an endophytic *Xylaria* sp. from *Ginkgo biloba*. *Food Chem.* **2007**, *105*, 548–554. [[CrossRef](#)]
151. Patil, M.P.; Patil, R.H.; Maheshwari, V.L. Biological activities and identification of bioactive metabolite from endophytic *Aspergillus flavus* L7 isolated from *Aegle marmelos*. *Curr. Microbiol.* **2015**, *71*, 39–48. [[CrossRef](#)]
152. El-Elimat, T.; Raja, H.A.; Graf, T.N.; Faeth, S.H.; Cech, N.B.; Oberlies, N.H. Flavonolignans from *Aspergillus iizukae*, a fungal endophyte of milk thistle (*Silybum marianum*). *J. Nat. Prod.* **2014**, *77*, 193–199. [[CrossRef](#)]
153. Gu, C.; Ma, H.; Ning, W.; Niu, L.; Han, H.; Yuan, X.; Fu, Y. Characterization, culture medium optimization and antioxidant activity of an endophytic vitexin-producing fungus *Dichotomopilus funicola* Y3 from pigeon pea [*Cajanus cajan* (L.) Millsp.]. *J. Appl. Microbiol.* **2018**, *125*, 1054–1065. [[CrossRef](#)]
154. Sato, F.; Matsukawa, Y.; Matsumoto, K.; Nishino, H.; Sakai, T. Apigenin induces morphological differentiation and G₂-M arrest in rat neuronal cells. *Biochem. Biophys. Res. Comm.* **1994**, *204*, 578–584. [[CrossRef](#)] [[PubMed](#)]
155. Viola, H.; Wasowski, C.; Levi de Stein, M.; Wolfman, C.; Silveira, R.; Dajas, F.; Medina, J.H.; Paladini, A.C. Apigenin, a component of *Matricaria recutita* flowers, is a central benzodiazepine receptors-ligand with anxiolytic effects. *Planta Med.* **1995**, *61*, 213–216. [[CrossRef](#)] [[PubMed](#)]
156. Salehi, B.; Venditti, A.; Sharifi-Rad, M.; Kręgiel, D.; Sharifi-Rad, J.; Durazzo, A.; Lucarini, M.; Santini, A.; Souto, E.B.; Novellino, E.; et al. The therapeutic potential of apigenin. *Int. J. Mol. Sci.* **2019**, *20*, 1305. [[CrossRef](#)] [[PubMed](#)]
157. Luo, M.; Liu, X.; Zu, Y.; Fu, Y.; Zhang, S.; Yao, L.; Efferth, T. Cajanol, a novel anticancer agent from pigeonpea [*Cajanus cajan* (L.) Millsp.] roots, induces apoptosis in human breast cancer cells through a ROS-mediated mitochondrial pathway. *Chem. Biol. Interact.* **2010**, *188*, 151–160. [[CrossRef](#)] [[PubMed](#)]
158. Fadus, M.C.; Lau, C.; Bikhchandani, J.; Lynch, H.T. Curcumin: An age-old anti-inflammatory and anti-neoplastic agent. *J. Tradit. Complement. Med.* **2017**, *7*, 339–346. [[CrossRef](#)] [[PubMed](#)]
159. Hassan, F.U.; Rehman, M.S.; Khan, M.S.; Ali, M.A.; Javed, A.; Nawaz, A.; Yang, C. Curcumin as an alternative epigenetic modulator: Mechanism of action and potential effects. *Front. Genet.* **2019**, *10*, 514. [[CrossRef](#)]
160. Chen, A.Y.; Chen, Y.C. A review of the dietary flavonoid, kaempferol on human health and cancer chemoprevention. *Food Chem.* **2013**, *138*, 2099–2107. [[CrossRef](#)]
161. Imran, M.; Salehi, B.; Sharifi-Rad, J.; Aslam Gondal, T.; Saeed, F.; Imran, A.; Shahbaz, M.; Tsouh Fokou, P.V.; Umair Arshad, M.; Khan, H.; et al. Kaempferol: A key emphasis to its anticancer potential. *Molecules* **2019**, *24*, 2277. [[CrossRef](#)]
162. Lopez-Lazaro, M. Distribution and biological activities of the flavonoid luteolin. *Mini Rev. Med. Chem.* **2009**, *9*, 31–59. [[CrossRef](#)]
163. Kim, J.M.; Kwon, C.S.; Son, K.H. Inhibition of alpha-glucosidase and amylase by luteolin, a flavonoid. *Biosci. Biotechnol. Biochem.* **2000**, *64*, 2458–2461. [[CrossRef](#)]

164. Srivastava, S.; Somasagara, R.R.; Hegde, M.; Nishana, M.; Tadi, S.K.; Srivastava, M.; Choudhary, B.; Raghavan, S.C. Quercetin, a natural flavonoid interacts with DNA, arrests cell cycle and causes tumor regression by activating mitochondrial pathway of apoptosis. *Sci. Rep.* **2016**, *6*, 24049. [[CrossRef](#)] [[PubMed](#)]
165. Colunga Biancatelli, R.M.L.; Berrill, M.; Catravas, J.D.; Marik, P.E. Quercetin and vitamin C: An experimental, synergistic therapy for the prevention and treatment of SARS-CoV-2 related disease (COVID-19). *Front. Immunol.* **2020**, *11*, 1451. [[CrossRef](#)] [[PubMed](#)]
166. Marunaka, Y.; Marunaka, R.; Sun, H.; Yamamoto, T.; Kanamura, N.; Inui, T.; Taruno, A. Actions of quercetin, a polyphenol, on blood pressure. *Molecules* **2017**, *22*, 209. [[CrossRef](#)] [[PubMed](#)]
167. Costa, L.G.; Garrick, J.M.; Roquè, P.J.; Pellacani, C. Mechanisms of neuroprotection by quercetin: Counteracting oxidative stress and more. *Oxid. Med. Cell. Longev.* **2016**, *2016*, 1–10. [[CrossRef](#)]
168. Ganeshpurkar, A.; Saluja, A.K. The pharmacological potential of rutin. *Saudi Pharm. J.* **2017**, *25*, 149–164. [[CrossRef](#)] [[PubMed](#)]
169. Enogieru, A.B.; Haylett, W.; Hiss, D.C.; Bardien, S.; Ekpo, O.E. Rutin as a potent antioxidant: Implications for neurodegenerative disorders. *Oxidat. Med. Cell. Long.* **2018**, *17*, 6241017. [[CrossRef](#)] [[PubMed](#)]
170. Ramasamy, K.; Agarwal, R. Multitargeted therapy of cancer by silymarin. *Cancer Lett.* **2008**, *269*, 352–362. [[CrossRef](#)]
171. Vargas-Mendoza, N.; Madrigal-Santillán, E.; Morales-González, Á.; Esquivel-Soto, J.; Esquivel-Chirino, C.; y González-Rubio, M.G.L.; Gayosso-de-Lucio, J.A.; Morales-González, J.A. Hepatoprotective effect of silymarin. *World J. Hepatol.* **2014**, *6*, 144–149. [[CrossRef](#)]
172. Dixit, N.; Baboota, S.; Kohli, K.; Ahmad, S.; Ali, J. Silymarin: A review of pharmacological aspects and bioavailability enhancement approaches. *Indian J. Pharmacol.* **2007**, *39*, 172. [[CrossRef](#)]
173. Karimi, G.; Vahabzadeh, M.; Lari, P.; Rashedinia, M.; Moshiri, M. “Silymarin”, a promising pharmacological agent for treatment of diseases. *Iran. J. Basic Med. Sci.* **2011**, *14*, 308.
174. He, M.; Min, J.W.; Kong, W.L.; He, X.H.; Li, J.X.; Peng, B.W. A review on the pharmacological effects of vitexin and isovitexin. *Fitoterapia* **2016**, *115*, 74–85. [[CrossRef](#)] [[PubMed](#)]
175. Chapela, I.H.; Petrini, O.; Hagmann, L. Monolignol glucosides as specific recognition messengers in fungus-plant symbioses. *Physiol. Mol. Plant Pathol.* **1991**, *39*, 289–298. [[CrossRef](#)]
176. Kong, P.; Zhang, L.; Guo, Y.; Lu, Y.; Lin, D. Phillyrin, a natural lignan, attenuates tumor necrosis factor α -mediated insulin resistance and lipolytic acceleration in 3T3-L1 adipocytes. *Planta Med.* **2014**, *80*, 880–886. [[CrossRef](#)] [[PubMed](#)]
177. Zhang, Q.; Wei, X.; Wang, J. Phillyrin produced by *Colletotrichum gloeosporioides*, an endophytic fungus isolated from *Forsythia suspensa*. *Fitoterapia* **2012**, *83*, 1500–1505. [[CrossRef](#)] [[PubMed](#)]
178. Yang, X.; Guo, S.; Zhang, L.; Shao, H. Select of producing podophyllotoxin endophytic fungi from podophyllin plant. *Nat. Prod. Res. Dev.* **2003**, *15*, 419–422.
179. Zeng, S.; Shao, H.; Zhang, L. An endophytic fungus producing a substance analogous to podophyllotoxin isolated from *Diphylleia sinensis*. *J. Microbiol.* **2004**, *24*, 1–2.
180. Lu, L.; He, J.; Yu, X.; Li, G.; Zhang, X. Studies on isolation and identification of endophytic fungi strain SC13 from pharmaceutical plant *Sabina vulgaris* Ant. and metabolites. *Acta Agric. Boreali-Occident. Sin.* **2006**, *15*, 85–89.
181. Eyberger, A.L.; Dondapati, R.; Porter, J.R. Endophyte fungal isolates from *Podophyllum peltatum* produce podophyllotoxin. *J. Nat. Prod.* **2006**, *69*, 1121–1124. [[CrossRef](#)]
182. Puri, S.C.; Nazir, A.; Chawla, R.; Arora, R.; Riyaz-ul-Hasan, S.; Amna, T.; Ahmed, B.; Verma, V.; Singh, S.; Sagar, R.; et al. The endophytic fungus *Trametes hirsuta* as a novel alternative source of podophyllotoxin and related aryl tetralin lignans. *J. Biotechnol.* **2006**, *122*, 494–510. [[CrossRef](#)]
183. Cao, L.; Huang, J.; Li, J. Fermentation conditions of *Sinopodophyllumhexandrum* endophytic fungus on production of podophyllotoxin. *Food Ferment. Ind.* **2007**, *33*, 28–32.
184. Kour, A.; Shawl, A.S.; Rehman, S.; Sultan, P.; Qazi, P.H.; Suden, P.; Khajuria, R.K.; Verma, V. Isolation and identification of an endophytic strain of *Fusarium oxysporum* producing podophyllotoxin from *Juniperus recurva*. *World. J. Microbiol. Biotechnol.* **2008**, *24*, 1115–1121. [[CrossRef](#)]
185. Kusari, S.; Lamshöft, M.; Spittler, M. *Aspergillus fumigatus* Fresenius, an endophytic fungus from *Juniperus communis* L. Horstmann as a novel source of the anticancer pro-drug deoxypodophyllotoxin. *J. Appl. Microbiol.* **2009**, *107*, 1019–1030. [[CrossRef](#)] [[PubMed](#)]
186. Nadeem, M.; Mauji, R.; Pravej, A.; Ahmad, M.M.; Mohammad, A.; Qurainy, F.A.; Khan, S.; Abidin, M.Z. *Fusarium solani*, P1, a new endophytic podophyllotoxin-producing fungus from roots of *Podophyllum hexandrum*. *Afr. J. Microbiol. Res.* **2012**, *6*, 2493–2499.
187. Arneaud, S.L.; Porter, J.R. Investigation and expression of the secoisolariciresinol dehydrogenase gene involved in podophyllotoxin biosynthesis. *Mol. Biotechnol.* **2015**, *57*, 961–973. [[CrossRef](#)]
188. Liang, Z.; Zhang, J.; Zhang, X.; Li, J.; Zhang, X.; Zhao, C. Endophytic fungus from *Sinopodophyllum emodi* (Wall.) Ying that produces Podophyllotoxin. *J. Chromatogr. Sci.* **2016**, *54*, 175–178.
189. Tan, X.; Zhou, Y.; Zhou, X.; Xia, X.; Wei, Y.; He, L.; Tang, H.; Yu, L. Diversity and bioactive potential of culturable fungal endophytes of *Dysosma versipellis*; a rare medicinal plant endemic to China. *Sci. Rep.* **2018**, *8*, 5929. [[CrossRef](#)]
190. Cheng, M.J.; Wu, M.D.; Chen, J.J.; Hsieh, S.Y.; Yuan, G.F.; Chen, I.S.; Chang, C.W. Secondary metabolites from the endophytic fungus of *Annulohyphoxylon ilanense*. *Chem. Nat. Compd.* **2013**, *49*, 523–525. [[CrossRef](#)]

191. Krishnan, S.S.C.; Subramanian, I.P.; Subramanian, S.P. Isolation, characterization of syringin, phenylpropanoid glycoside from *Musa paradisiaca* tepal extract and evaluation of its antidiabetic effect in streptozotocin-induced diabetic rats. *Biomed. Prev. Nutr.* **2014**, *4*, 105–111. [[CrossRef](#)]
192. Canel, C.; Moraes, R.M.; Dayan, F.E.; Ferreira, D. Podophyllotoxin. *Phytochemistry* **2000**, *54*, 115–120. [[CrossRef](#)]
193. Zhou, L.; Cao, X.; Yang, C.; Wu, X.; Zhang, L. Endophytic fungi of *Paris polyphylla* var. *yunnanensis* and steroid analysis in the fungi. *Nat. Prod. Res. Dev.* **2004**, *16*, 198–200.
194. Cao, X.; Li, J.; Zhou, L.; Xu, L.; Li, J.; Zhao, J. Determination of diosgenin content of the endophytic fungi from *Paris polyphylla* var. *yunnanensis* by using an optimum ELISA. *Nat. Prod. Res. Dev.* **2007**, *19*, 1020–1023.
195. Ding, C.H.; Du, X.W.; Xu, Y.; Xu, X.M.; Mou, J.C.; Yu, D.; Wu, J.K.; Meng, F.J.; Liu, Y.; Wang, W.L.; et al. Screening for differentially expressed genes in endophytic fungus strain 39 during co-culture with herbal extract of its host *Dioscorea nipponica* Makino. *Curr. Microbiol.* **2014**, *69*, 517–524. [[CrossRef](#)] [[PubMed](#)]
196. Wu, H.; Yang, H.; You, X.; Li, Y. Isolation and characterization of saponin-producing fungal endophytes from *Aralia elata* in Northeast China. *Int. J. Mol. Sci.* **2012**, *13*, 16255–16266. [[CrossRef](#)] [[PubMed](#)]
197. Wu, H.; Yang, H.Y.; You, X.L.; Li, Y.H. Diversity of endophytic fungi from roots of *Panax ginseng* and their saponin yield capacities. *SpringerPlus* **2013**, *2*, 107. [[CrossRef](#)]
198. Jin, Z.; Gao, L.; Zhang, L.; Liu, T.; Yu, F.; Zhang, Z.; Guo, Q.; Wang, B. Antimicrobial activity of saponins produced by two novel endophytic fungi from *Panax notoginseng*. *Nat. Prod. Res.* **2017**, *31*, 2700–2703. [[CrossRef](#)]
199. Parthasarathy, R.; Sathiyabama, M. Gymnemenin-producing endophytic fungus isolated from a medicinal plant *Gymnema sylvestre* R. Br. *Appl. Biochem. Biotechnol.* **2014**, *172*, 3141–3152. [[CrossRef](#)]
200. Govindappa, M.; Bharath, N.; Shruthi, H.B.; Santoyo, G. In vitro antioxidant activity and phytochemical screening of endophytic extracts of *Crotalaria pallida*. *Free Radic. Antioxid.* **2011**, *1*, 79–86. [[CrossRef](#)]
201. Govindappa, M.; Channabasava, R.; Sowmya, D.V.; Meenakshi, J.; Shreevidya, M.R.; Lavanya, A.; Santoyo, G.; Sadananda, T.S. Phytochemical screening, antimicrobial and in vitro anti-inflammatory activity of endophytic extracts from *Loranthus* sp. *Pharmaco. J.* **2011**, *3*, 82–90. [[CrossRef](#)]
202. Sadananda, T.S.; Nirupama, R.; Chaithra, K.; Govindappa, M.; Chandrappa, C.P.; Vinay Raghavendra, B. Antimicrobial and antioxidant activities of endophytes from *Tabebuia argentea* and identification of anticancer agent (lapachol). *J. Med. Plants Res.* **2011**, *5*, 3643–3652.
203. Dhankhar, S.; Kumar, S.; Dhankhar, S.; Yadav, J.P. Antioxidant activity of fungal endophytes isolated from *Salvadoraoleoides* Decne. *Int. J. Pharm. Pharm. Sci.* **2012**, *4*, 381–385.
204. Prabavathy, D.; Nachiyar, C. Cytotoxic potential and phytochemical analysis of *Justicia beddomei* and its endophytic *Aspergillus* sp. *Asian J. Pharm. Clin. Res.* **2013**, *6*, 159–161.
205. Pragathi, D.; Vijaya, T.; Mouli, K.C.; Anitha, D. Diversity of fungal endophytes and their bioactive metabolites from endemic plants of Tirumala hills–Seshachalam biosphere reserve. *Afr. J. Biotechnol.* **2013**, *12*, 4317–4323.
206. Saraswaty, V.; Srikanth, Y.; Simbiyani, N.A.; Setiyanto, H.; Udin, Z. Antioxidant activity and total phenolic content of endophytic fungus *Fennellia nivea* NRRL 5504. *Pakistan J. Biol. Sci.* **2013**, *16*, 1574–1578. [[CrossRef](#)] [[PubMed](#)]
207. Karunai Selvi, B.; Balagengatharathilagam, P. Isolation and screening of endophytic fungi from medicinal plants of Virudhunagar district for antimicrobial activity. *Int. J. Sci. Nat.* **2014**, *5*, 147–155.
208. Yadav, M.; Yadav, A.; Yadav, J.P. In vitro antioxidant activity and total phenolic content of endophytic fungi isolated from *Eugenia jambolana* Lam. *Asian Pac. J. Trop. Med.* **2014**, *7*, 256–261. [[CrossRef](#)]
209. Nath, A.; Chattopadhyay, A.; Joshi, S.R. Biological activity of endophytic fungi of *Rauwolfia serpentina* Benth: An ethnomedicinal plant used in folk medicines in Northeast India. *Proc. Natl. Acad. Sci. India Sect. B Biol. Sci.* **2015**, *85*, 233–240. [[CrossRef](#)]
210. Jesus, M.; Martini, A.P.; Gallardo, E.; Silvestre, S. Diosgenin: Recent highlights on pharmacology and analytical methodology. *J. Anal. Methods Chem.* **2016**, *2016*, 1–16. [[CrossRef](#)]
211. Gardner, D.R.; Panter, K.E.; Stegelmeier, B.L. Implication of agathic acid from Utah juniper bark as an abortifacient compound in cattle. *J. Appl. Toxicol.* **2010**, *30*, 115–119. [[CrossRef](#)]
212. Izumi, E.; Ueda-Nakamura, T.; Veiga, V.F., Jr.; Pinto, A.C.; Nakamura, C.V. Terpenes from *Copaifera* demonstrated in vitro antiparasitic and synergic activity. *J. Med. Chem.* **2012**, *55*, 2994–3001. [[CrossRef](#)]
213. Yuan, L.; Zhao, P.J.; Ma, J.; Lu, C.H.; Shen, Y.M. Labdane tetranorlabdane diterpenoids from *Botryosphaeria* sp. MHF, an endophytic fungus of *Maytenus hookeri*. *Helv. Chim. Acta* **2009**, *92*, 1118–1125. [[CrossRef](#)]
214. Kamdem, R.S.; Wang, H.; Wafo, P.; Ebrahim, W.; Özkaya, F.C.; Makhoulfi, G.; Janiak, C.; Sureechatchaiyan, P.; Kassack, M.U.; Lin, W.; et al. Induction of new metabolites from the endophytic fungus *Bionectria* sp. through bacterial co-culture. *Fitoterapia* **2018**, *124*, 132–136. [[CrossRef](#)] [[PubMed](#)]
215. Yan, C.; Liu, W.; Li, J.; Deng, Y.; Chen, S.; Liu, H. Bioactive terpenoids from *Santalum album* derived endophytic fungus *Fusarium* sp. YD-2. *RSC Adv.* **2018**, *8*, 14823–14828. [[CrossRef](#)]
216. Huang, W.Y.; Cai, Y.Z.; Xing, J.; Corke, H.; Sun, M. A potential antioxidant resource: Endophytic fungi from medicinal plants. *Econ. Bot.* **2007**, *61*, 14–30. [[CrossRef](#)]
217. Gupta, S.; Bhatt, P.; Chaturvedi, P. Determination and quantification of asiaticoside in endophytic fungus from *Centella asiatica* (L.) Urban. *World J. Microbiol. Biotechnol.* **2018**, *34*, 111. [[CrossRef](#)] [[PubMed](#)]

218. Kusari, S.; Verma, V.C.; Lamshoeft, M.; Spitteller, M. An endophytic fungus from *Azadirachta indica* A. Juss. that produces azadirachtin. *World J. Microbiol. Biotechnol.* **2012**, *28*, 1287–1294. [[CrossRef](#)]
219. Qian, Y.X.; Kang, J.C.; Luo, Y.K.; Zhao, J.J.; He, J.; Geng, K. A Bilobalide-producing endophytic fungus, *Pestalotiopsis uvicola* from medicinal plant *Ginkgo biloba*. *Curr. Microbiol.* **2016**, *73*, 280–286. [[CrossRef](#)]
220. Chen, M.; Yang, L.; Li, Q.; Shen, Y.; Shao, A.; Lin, S.; Huang, L. Volatile metabolites analysis and molecular identification of endophytic fungi bn12 from *Cinnamomum camphora* var. *borneol*. *Chin. J. Chin. Mater. Med.* **2011**, *36*, 3217–3221.
221. Suwannarach, N.; Kumla, J.; Bussaban, B.; Nuangmek, W.; Matsui, K.; Lumyong, S. Biofumigation with the endophytic fungus *Nodulisporium* spp. CMU-UPE34 to control postharvest decay of citrus fruit. *Crop. Prot.* **2013**, *45*, 63–70. [[CrossRef](#)]
222. Tomsheck, A.R.; Strobel, G.A.; Booth, E.; Geary, B.; Spakowicz, D.; Knighton, B.; Floerchinger, C.; Sears, J.; Liarzi, O.; Ezra, D. *Hypoxylon* sp., an endophyte of *Persea indica*, producing 1,8-cineole and other bioactive volatiles with fuel potential. *Microb. Ecol.* **2010**, *60*, 903–914. [[CrossRef](#)]
223. Hassan, S.R.; Strobel, G.A.; Geary, B.; Sears, J. An endophytic *Nodulisporium* sp. from Central America producing volatile organic compounds with both biological and fuel potential. *J. Microbiol. Biotechnol.* **2013**, *23*, 29–35. [[CrossRef](#)]
224. Nigg, J.; Strobel, G.; Knighton, W.B.; Hilmer, J.; Geary, B.; Riyaz-UI-Hassan, S.; Harper, J.K.; Valenti, D.; Wang, Y. Functionalized para-substituted benzenes as 1, 8-cineole production modulators in an endophytic *Nodulisporium* species. *Microbiology* **2014**, *160*, 1772–1782. [[CrossRef](#)] [[PubMed](#)]
225. Wang, K.Y.; Strobel, G.A.; Yan, D.H. The production of 1, 8-cineole, a potential biofuel, from an endophytic strain of *Annulohypoxylon* sp. FPYF3050 when grown on agricultural residues. *J. Sustain. Bioenergy Syst.* **2017**, *7*, 65–84. [[CrossRef](#)]
226. Cui, Y.; Yi, D.; Bai, X.; Sun, B.; Zhao, Y.; Zhang, Y. Ginkgolide B produced endophytic fungus (*Fusarium oxysporum*) isolated from *Ginkgo biloba*. *Fitoterapia* **2012**, *83*, 913–920. [[CrossRef](#)] [[PubMed](#)]
227. Wu, M.D.; Cheng, M.J.; Chen, I.S.; Su, Y.S.; Hsieh, S.Y.; Chang, H.S.; Chang, C.W.; Yuan, G.F. Phytochemical investigation of *Annulohypoxylon ilanense*, an endophytic fungus derived from *Cinnamomum* species. *Chem. Biodivers.* **2013**, *10*, 493–505. [[CrossRef](#)] [[PubMed](#)]
228. Caruso, M.; Colombo, A.L.; Fedeli, L.; Pavesi, A.; Quaroni, S.; Saracchi, M.; Ventrella, G. Isolation of endophytic fungi and actinomycetes taxane producers. *Ann. Microbiol.* **2000**, *50*, 3–14.
229. Staniek, A.; Woerdenbag, H.J.; Kayser, O. Screening the endophytic flora of *Wollemia nobilis* for alternative paclitaxel sources. *J. Plant Interact.* **2010**, *5*, 189–195. [[CrossRef](#)]
230. Qiu, D.; Huang, M.; Fang, X.; Zhu, C.; Zhu, Z. Isolation of an endophytic fungus associated with *Taxus yunnanensis* Cheng et LK Fu. *Acta Mycol. Sin.* **1994**, *13*, 314.
231. Li, J.Y.; Strobel, G.A.; Sidhu, R.; Hess, W.M.; Ford, E.J. Endophytitaxol-producing fungi from bald cypress, *Taxodium distichum*. *Microbiology* **1996**, *142*, 2223–2226. [[CrossRef](#)]
232. Strobel, G.A.; Hess, W.M.; Ford, E.; Sidhu, R.S.; Yang, X. Taxol from fungal endophytes and the issue of biodiversity. *J. Ind. Microbiol. Biotechnol.* **1996**, *17*, 417–423. [[CrossRef](#)]
233. Strobel, G.; Yang, X.; Sears, J.; Kramer, R.; Sidhu, R.S.; Hess, W.M. Taxol from *Pestalotiopsis microspora*, an endophytic fungus of *Taxus wallachiana*. *Microbiology* **1996**, *142*, 435–440. [[CrossRef](#)]
234. Strobel, G.A.; Hess, W.M.; Li, J.Y.; Ford, E.; Sears, J.; Sidhu, R.S.; Summerell, B. *Pestalotiopsis guepinii*, a taxol-producing endophyte of the Wollemi pine, *Wollemia nobilis*. *Aust. J. Bot.* **1997**, *45*, 1073–1082. [[CrossRef](#)]
235. Li, J.Y.; Sidhu, R.S.; Ford, E.J.; Long, D.M.; Hess, W.M.; Strobel, G.A. The induction of taxol production in the endophytic fungus-*Periconia* sp. from *Torreya grandifolia*. *J. Ind. Microbiol. Biotechnol.* **1998**, *20*, 259–264. [[CrossRef](#)]
236. Bashyal, B. *Seimatoantlerium nepalense*, an endophytic taxol producing coelomycete from Himalayan yew (*Taxus wallachiana*). *Mycotaxon* **1999**, *72*, 33–42.
237. Kim, S.U.; Strobel, G.A.; Ford, E. Screening of taxol-producing endophytic fungi from *Ginkgo biloba* and *Taxus cuspidata* in Korea. *Agric. Chem. Biotechnol.* **1999**, *42*, 97–99.
238. Stierle, A.; Stierle, D.; Stierle, S. Bioactive compounds from four endophytic *Penicillium* sp. of a northwest pacific yew tree. *Nat. Prod. Chem.* **2000**, *24*, 933–977.
239. Wang, J.; Li, G.; Lu, H.; Zheng, Z.; Huang, Y.; Su, W. Taxol from *Tubercularia* sp. strain TF5, an endophytic fungus of *Taxus mairei*. *FEMS Microbiol. Lett.* **2000**, *193*, 249–253. [[CrossRef](#)]
240. Strobel, G.A.; Hess, W.M.; Baird, G.; Ford, E.; Li, J.Y.; Sidhu, R.S. *Stegolerium kukenani* gen. et sp. nov. an endophytic, taxol producing fungus from the *Roraima* and *Kukenan tepuis* of Venezuela. *Mycotaxon* **2001**, *78*, 353–361.
241. Wan, B.; Li, A.M.; Wang, X.L. Separation of a fungus producing taxol. *Sci. China Ser. C* **2001**, *44*, 156–160. [[CrossRef](#)]
242. Shrestha, K.; Strobel, G.A.; Shrivastava, S.P.; Gewali, M.B. Evidence for paclitaxel from three new endophytic fungi of Himalayan yew of Nepal. *Planta Med.* **2001**, *67*, 374–376. [[CrossRef](#)]
243. Zhao, K.; Zhou, D.P.; Ping, W.X.; Ge, J. Study on the preparation and regeneration of protoplast from taxol-producing fungus *Nodulisporium sylviforme*. *Nat. Sci.* **2004**, *2*, 52–59.
244. Guo, B.H.; Wang, Y.C.; Zhou, X.W.; Hu, K.; Tan, F.; Miao, Z.Q.; Tang, K.X. An endophytic taxol-producing fungus BT2 isolated from *Taxus chinensis* var. *mairei*. *Afr. J. Biotechnol.* **2006**, *5*, 875–877.
245. Hu, K.; Tan, F.; Tang, K.; Zhu, S.; Wang, W. Isolation and screening of endophytic fungi synthesizing taxol from *Taxus chinensis* var. *mairei*. *J. Southwest China Norm. Univ. (Nat. Sci. Ed.)* **2006**, *31*, 134–137.

246. Liu, J.J.; Gong, H.X.; Yang, D.L.; Chen, S.J.; Yang, L. Study on endophytic fungi producing taxol isolated from *Taxus yunnanensis*. *Prog. Mod. Biomed.* **2006**, *6*, 53–55.
247. Xu, F.; Tao, W.; Chang, L.; Guo, L. Strain improvement and optimization of the media of taxol-producing fungus *Fusarium mairei*. *Biochem. Eng. J.* **2006**, *31*, 67–73. [[CrossRef](#)]
248. Gangadevi, V.; Muthumary, J. Endophytic fungal diversity from young, mature and senescent leaves of *Ocimum basilicum* L. with special reference to taxol production. *Indian J. Sci. Technol.* **2007**, *1*, 1–12. [[CrossRef](#)]
249. Zhou, X.; Wang, Z.; Jiang, K.; Wei, Y.; Lin, J.; Sun, X.; Tang, K. Screening of taxol-producing endophytic fungi from *Taxus chinensis* var. *mairei*. *Appl. Biochem. Microbiol.* **2007**, *43*, 439–443. [[CrossRef](#)]
250. Chakravarthi, B.V.; Das, P.; Surendranath, K.; Karande, A.A.; Jayabaskaran, C. Production of paclitaxel by *Fusarium solani* isolated from *Taxus celebica*. *J. Biosci.* **2008**, *33*, 259–267. [[CrossRef](#)]
251. Gangadevi, V.; Murugan, M.; Muthumary, J. Taxol determination from *Pestalotiopsis paucisetata*, a fungal endophyte of a medicinal plant. *Chin. J. Biotechnol.* **2008**, *24*, 1433–1438. [[CrossRef](#)]
252. Gangadevi, V.; Muthumary, J. Taxol, an anticancer drug produced by an endophytic fungus *Bartalinia robillardoides* Tassi, isolated from a medicinal plant, *Aegle marmelos* Correa ex Roxb. *World J. Microbiol. Biotechnol.* **2008**, *24*, 717–724. [[CrossRef](#)]
253. Gangadevi, V.; Muthumary, J. Isolation of *Colletotrichum gloeosporioides*, a novel endophytic taxol-producing fungus from the leaves of a medicinal plant, *Justicia gendarussa*. *Mycol. Balc.* **2008**, *5*, 1–4.
254. Gogoi, D.K.; Deka Boruah, H.P.; Saikia, R.; Bora, T.C. Optimization of process parameters for improved production of bioactive metabolite by a novel endophytic fungus *Fusarium* sp. DF2 isolated from *Taxus wallichiana* of North East India. *World J. Microbiol. Biotechnol.* **2008**, *24*, 79–87. [[CrossRef](#)]
255. Kumaran, R.S.; Muthumary, J.; Hur, B.K. Taxol from *Phyllosticta citricarpa*, a leaf spot fungus of the angiosperm *Citrus medica*. *J. Biosci. Bioeng.* **2008**, *106*, 103–106. [[CrossRef](#)] [[PubMed](#)]
256. Kumaran, R.S.; Muthumary, J.; Hur, B.K. Isolation and identification of taxol, an anticancer drug from *Phyllosticta melochiae* Yates, an endophytic fungus of *Melochia corchorifolia* L. *Food Sci. Biotechnol.* **2008**, *17*, 1246–1253.
257. Kumaran, R.S.; Muthumary, J.; Hur, B. Production of taxol from *Phyllosticta spinarum*, an endophytic fungus of *Cupressus* sp. *Eng. Life Sci.* **2008**, *8*, 438–446. [[CrossRef](#)]
258. Li, C.T.; Li, Y.; Wang, Q.J.; Sung, C.K. Taxol production by *Fusarium arthrosporioides* isolated from yew, *Taxus cuspidata*. *J. Med. Biochem.* **2008**, *27*, 454–458. [[CrossRef](#)]
259. Sun, D.; Ran, X.; Wang, J. Isolation and identification of a taxol producing endophytic fungus from *Podocarpus*. *Acta Microbiol. Sin.* **2008**, *48*, 589–595.
260. Venkatachalam, R.; Subban, K.; Paul, M.J. Taxol from *Botryodiplodia theobromae* (BT 115)-an endophytic fungus of *Taxus baccata*. *J. Biotechnol.* **2008**, *136*, 189–190. [[CrossRef](#)]
261. Zhao, K.; Zhao, L.; Jin, Y.; Wei, H.; Ping, W.; Zhou, D. Isolation of a taxol-producing endophytic fungus and inhibiting effect of the fungus metabolites on HeLa cell. *Mycosystema* **2008**, *27*, 735–744.
262. Deng, B.W.; Liu, K.H.; Chen, W.Q.; Ding, X.W.; Xie, X.C. *Fusarium solani*, Tax-3, a new endophytic taxol-producing fungus from *Taxus chinensis*. *World J. Microb. Biotechnol.* **2009**, *25*, 139–143. [[CrossRef](#)]
263. Gangadevi, V.; Muthumary, J. A novel endophytic taxol-producing fungus *Chaetomella raphigera* isolated from a medicinal plant, *Terminalia arjuna*. *Appl. Biochem. Biotechnol.* **2009**, *158*, 675–684. [[CrossRef](#)]
264. Gangadevi, V.; Muthumary, J. Taxol production by *Pestalotiopsis terminaliae*, an endophytic fungus of *Terminalia arjuna* (arjun tree). *Biotechnol. Appl. Biochem.* **2009**, *52*, 9–15. [[CrossRef](#)]
265. Kumaran, R.S.; Hur, B.K. Screening of species of the endophytic fungus *Phomopsis* for the production of the anticancer drug taxol. *Biotechnol. Appl. Biochem.* **2009**, *54*, 21–30. [[CrossRef](#)] [[PubMed](#)]
266. Kumaran, R.S.; Muthumary, J.; Kim, E.K.; Hur, B.K. Production of taxol from *Phyllosticta dioscoreae*, a leaf spot fungus isolated from *Hibiscus rosa-sinensis*. *Biotechnol. Bioprocess* **2009**, *14*, 76–83. [[CrossRef](#)]
267. Liu, K.; Ding, X.; Deng, B.; Chen, W. Isolation and characterization of endophytic taxol-producing fungi from *Taxus chinensis*. *J. Ind. Microbiol. Biotechnol.* **2009**, *36*, 1171–1177. [[CrossRef](#)] [[PubMed](#)]
268. Miao, Z.; Wang, Y.; Yu, X.; Guo, B.; Tang, K. A new endophytic taxane production fungus from *Taxus chinensis*. *Appl. Biochem. Microbiol.* **2009**, *45*, 81–86. [[CrossRef](#)]
269. Nithya, K.; Muthumary, J. Growth studies of *Colletotrichum gloeosporioides* (Penz.) Sacc.—A taxol producing endophytic fungus from *Plumeria acutifolia*. *Indian J. Sci. Technol.* **2009**, *2*, 14–19. [[CrossRef](#)]
270. Sreekanth, D.; Syed, A.; Sarkar, S.; Sarkar, D.; Santhakumari, B.; Ahmad, A.; Khan, I. Production, purification and characterization of taxol and 10DAB III from a new endophytic fungus *Gliocladium* sp. isolated from the Indian yew tree, *Taxus baccata*. *J. Microbiol. Biotechnol.* **2009**, *19*, 1342–1347. [[CrossRef](#)] [[PubMed](#)]
271. Srinivasan, K.; Muthumary, J. Taxol production from *Pestalotiopsis* sp. an endophytic fungus isolated from *Catharanthus roseus*. *J. Ecobiotechnol.* **2009**, *1*, 28–31.
272. Zhang, P.; Zhou, P.P.; Yu, L.J. An endophytic taxol-producing fungus from *Taxus x media*, *Aspergillus candidus* MD3. *FEMS Microbiol. Lett.* **2009**, *293*, 155–159. [[CrossRef](#)]
273. Zhang, P.; Zhou, P.P.; Yu, L.J. An endophytic taxol-producing fungus from *Taxus media*, *Cladosporium cladosporioides* MD2. *Curr. Microbiol.* **2009**, *59*, 227–232. [[CrossRef](#)]

274. Zhao, K.; Ping, W.; Li, Q.; Hao, S.; Zhao, L.; Gao, T.; Zhou, D. *Aspergillus niger* var. *taxi*, a new species variant of taxol-producing fungus isolated from *Taxus cuspidata* in China. *J. Appl. Microbiol.* **2009**, *107*, 1202–1207. [CrossRef]
275. Zhou, X.; Zheng, W.; Zhu, H. Identification of a taxol-producing endophytic fungus EFY-36. *Afr. J. Biotechnol.* **2009**, *8*, 2623–2625.
276. Kumaran, R.S.; Kim, H.J.; Hur, B.K. Taxol promising fungal endophyte, *Pestalotiopsis* species isolated from *Taxus cuspidata*. *J. Biosci. Bioeng.* **2010**, *110*, 541–546. [CrossRef] [PubMed]
277. Vennila, R.; Thirunavukkarasu, S.V.; Muthumary, J. In-vivo studies on anticancer activity of taxol isolated from an endophytic fungus *Pestalotiopsis pauciseta* Sacc. VM1. *Asian J. Pharm. Clin. Res.* **2010**, *3*, 30–34.
278. Pandi, M.; Kumaran, R.S.; Choi, Y.K.; Kim, H.J.; Muthumary, J. Isolation and detection of taxol, an anticancer drug produced from *Lasiodiplodia theobromae*, an endophytic fungus of the medicinal plant *Morinda citrifolia*. *Afr. J. Biotechnol.* **2011**, *10*, 1428–1435.
279. Soca-Chafre, G.; Rivera-Orduña, F.N.; Hidalgo-Lara, M.E.; Hernandez-Rodriguez, C.; Marsch, R.; Flores-Cotera, L.B. Molecular phylogeny and paclitaxel screening of fungal endophytes from *Taxus globosa*. *Fungal Biol.* **2011**, *115*, 143–156. [CrossRef]
280. Soliman, S.S.M.; Tsao, R.; Raizada, M.N. Chemical inhibitors suggest endophytic fungal paclitaxel is derived from both mevalonate and non-mevalonate-like pathways. *J. Nat. Prod.* **2011**, *74*, 2497–2504. [CrossRef] [PubMed]
281. Wang, Y.; Tang, K. A new endophytic taxol- and baccatin III-producing fungus isolated from *Taxus chinensis* var. *mairei*. *Afr. J. Biotechnol.* **2011**, *10*, 16379–16386.
282. Mirjalili, M.H.; Farzaneh, M.; Bonfill, M.; Rezadoost, H.; Ghassempour, A. Isolation and characterization of *Stemphylium sedicola* SBU-16 as a new endophytic taxol-producing fungus from *Taxus baccata* grown in Iran. *FEMS Microbiol. Lett.* **2012**, *328*, 122–129. [CrossRef]
283. Senthilkumar, N.; Murugesan, S.; Mohan, V.; Muthumary, J. Taxol producing fungal endophyte, *Colletotrichum gleosporioides* (Penz.) from *Tectona grandis* L. *Curr. Biotica.* **2013**, *7*, 8–15.
284. Wu, L.S.; Hu, C.L.; Han, T.; Zheng, C.J.; Ma, X.Q.; Rahman, K.; Qin, L.P. Cytotoxic metabolites from *Perenniporiaatephropora*, an endophytic fungus from *Taxus chinensis* var. *mairei*. *Appl. Microbiol. Biotechnol.* **2013**, *97*, 305–315. [CrossRef] [PubMed]
285. Xiong, Z.Q.; Yang, Y.Y.; Zhao, N.; Wang, Y. Diversity of endophytic fungi and screening of fungal paclitaxel producer from *Angiojap yew*, *Taxus x media*. *BMC Microbiol.* **2013**, *13*, 71. [CrossRef] [PubMed]
286. Kumaran, R.S.; Choi, Y.K.; Lee, S.; Jeon, H.J.; Jung, H.; Kim, H.J. Isolation of taxol, an anticancer drug produced by the endophytic fungus, *Phoma betae*. *Afr. J. Biotechnol.* **2014**, *11*, 950–960.
287. Michalczyk, A.; Cieniecka-Rosłonkiewicz, A.; Cholewińska, M. Plant endophytic fungi as a source of paclitaxel. *Herba Pol. J.* **2014**, *60*, 22–33. [CrossRef]
288. Raj, K.G.; Rajapriya, P.; Muthumary, J.; Pandi, M. Molecular identification and characterization of the taxol-producing *Colletotrichum gloeosporioides* from *Moringa oleifera* Linn. In *Microbial Diversity and Biotechnology in Food Security*; Kharwar, R.N., Upadhyay, R., Dubey, N., Raghuvanshi, R., Eds.; Springer: New Delhi, India, 2014; pp. 111–120.
289. Wang, Y.; Ma, Z.; Hu, F.; Fan, M.; Li, Z. Isolation and screening of endophytic fungi producing taxol from *Taxus chinensis* of Huangshan. *Nat. Prod. Res. Dev.* **2014**, *26*, 1624–1627.
290. Yang, Y.; Zhao, H.; Barrero, R.A.; Zhang, B.; Sun, G.; Wilson, I.W.; Xie, F.; Walker, K.D.; Parks, J.W.; Bruce, R.; et al. Genome sequencing and analysis of the paclitaxel-producing endophytic fungus *Penicillium aurantiogriseum* NRRL 62431. *BMC Genom.* **2014**, *15*, 69. [CrossRef]
291. Isman, M.B. Botanical insecticides, deterrents, and repellents in modern agriculture and an increasingly regulated world. *Annu. Rev. Entomol.* **2006**, *51*, 45–66. [CrossRef]
292. Zhao, J.; Shan, T.; Mou, Y.; Zhou, L. Plant-derived bioactive compounds produced by endophytic fungi. *Mini Rev. Med. Chem.* **2011**, *11*, 159–168. [CrossRef]
293. Sathiyabama, M.; Parthasarathy, R. Withanolide production by fungal endophyte isolated from *Withania somnifera*. *Nat. Prod. Res.* **2018**, *32*, 1573–1577. [CrossRef]
294. Nibret, E.; Youns, M.; Krauth-Siegel, R.L.; Wink, M. Biological activities of xanthatin from *Xanthium strumarium* leaves. *Phytother. Res.* **2011**, *25*, 1883–1890. [CrossRef]
295. Xu, L.L.; Han, T.; Wu, J.Z.; Zhang, Q.Y.; Zhang, H.; Huang, B.K.; Rahman, K.; Qin, L.P. Comparative research of chemical constituents, antifungal and antitumor properties of ether extracts of *Panax ginseng* and its endophytic fungus. *Phytomedicine* **2009**, *16*, 609–616. [CrossRef] [PubMed]
296. Woodrow, C.J.; Haynes, R.K.; Krishna, S. Artemisinins. *Postgrad Med. J.* **2005**, *81*, 71–78. [CrossRef] [PubMed]
297. Q&A on Artemisinin Resistance. Available online: https://www.who.int/malaria/media/artemisinin_resistance_qa/en/ (accessed on 17 September 2020).
298. Das, A.K. Anticancer effect of antimalarial artemisinin compounds. *Ann. Med. Health Sci. Res.* **2015**, *5*, 93–102. [CrossRef] [PubMed]
299. O’neill, P.M.; Barton, V.E.; Ward, S.A. The molecular mechanism of action of artemisinin—The debate continues. *Molecules* **2010**, *15*, 1705–1721. [CrossRef] [PubMed]
300. Bridgford, J.L.; Xie, S.C.; Cobbold, S.A.; Pasaje, C.F.; Herrmann, S.; Yang, T.; Gillett, D.L.; Dick, L.R.; Ralph, S.A.; Dogovski, C.; et al. Artemisinin kills malaria parasites by damaging proteins and inhibiting the proteasome. *Nat. Commun.* **2018**, *9*, 1–9. [CrossRef]
301. Usai, S.; Grazi, L.; Bussone, G. Gingkolide B as migraine preventive treatment in young age: Results at 1-year follow-up. *Neurol. Sci.* **2011**, *1*, 197–199. [CrossRef]

302. Nutrition Business Journal Annual Report. *Nutr. Bus. J.* **2012**. Available online: <http://nutritionbusinessjournal.com/> (accessed on 9 December 2014).
303. Kiewert, C.; Kumar, V.; Hildmann, O.; Hartmann, J.; Hillert, M.; Klein, J. Role of glycine receptors and glycine release for the neuroprotective activity of bilobalide. *Brain Res.* **2008**, *27*, 143–150. [[CrossRef](#)]
304. Michelle, G.; Sharron, D. Bilobalide, a unique constituent of *Ginkgo biloba*, inhibits inflammatory pain in rats. *Behav. Pharmacol.* **2013**, *24*, 298–306.
305. Baker, M.A.; Demoret, R.M.; Ohtawa, M.; Shenvi, R.A. Concise asymmetric synthesis of (–)-bilobalide. *Nature* **2019**, *575*, 643–646. [[CrossRef](#)]
306. Guo, M.; Suo, Y.; Gao, Q.; Du, H.; Zeng, W.; Wang, Y.; Hu, X.; Jiang, X. The protective mechanism of Ginkgolides and Ginkgo flavonoids on the TNF- α induced apoptosis of rat hippocampal neurons and its mechanisms in vitro. *Heliyon* **2015**, *1*, e00020. [[CrossRef](#)] [[PubMed](#)]
307. Feng, Z.; Sun, Q.; Chen, W.; Bai, Y.; Hu, D.; Xie, X. The neuroprotective mechanisms of ginkgolides and bilobalide in cerebral ischemic injury: A literature review. *Mol. Med.* **2019**, *25*, 1–8. [[CrossRef](#)] [[PubMed](#)]
308. Wani, M.C.; Horwitz, S.B. Nature as a remarkable chemist: A personal story of the discovery and development of Taxol. *Anticancer Drugs* **2014**, *25*, 482–487. [[CrossRef](#)] [[PubMed](#)]
309. Brito, D.A.; Yang, Z.; Rieder, C.L. Microtubules do not promote mitotic slippage when the spindle assembly checkpoint cannot be satisfied. *J. Cell Biol.* **2008**, *182*, 623–629. [[CrossRef](#)] [[PubMed](#)]
310. Wang, Q.; Fu, Y.; Gao, J.; Wang, Y.; Li, X.; Zhang, A. Preliminary isolation and screening of the endophytic fungi from *Melia azedarach* L. *Acta Agric. Boreali-Occident. Sin.* **2007**, *16*, 224–227.
311. Jin, Y.H.; Kwon, S.; Choi, J.G.; Cho, W.K.; Lee, B.; Ma, J.Y. Toosendanin from *Melia fructus* suppresses influenza A virus infection by altering nuclear localization of viral polymerase PA protein. *Front. Pharmacol.* **2019**, *10*, 25. [[CrossRef](#)]
312. Zhang, T.; Li, J.; Yin, F.; Lin, B.; Wang, Z.; Xu, J.; Wang, H.; Zuo, D.; Wang, G.; Hua, Y.; et al. Toosendanin demonstrates promising antitumor efficacy in osteosarcoma by targeting STAT3. *Oncogene* **2017**, *36*, 6627–6639. [[CrossRef](#)]
313. Zhang, S.; Cao, L.; Wang, Z.; Li, Z.; Ma, J. Anti-cancer effect of toosendanin and its underlying mechanisms. *J. Asian Nat. Prod. Res.* **2019**, *21*, 270–283. [[CrossRef](#)]
314. Gao, T.; Xie, A.; Liu, X.; Zhan, H.; Zeng, J.; Dai, M.; Zhang, B. Toosendanin induces the apoptosis of human Ewing's sarcoma cells via the mitochondrial apoptotic pathway. *Mol. Med. Rep.* **2019**, *20*, 135–140. [[CrossRef](#)]
315. Kovács, A.; Vasas, A.; Forgo, P.; Réthy, B.; Zupkó, I.; Hohmann, J. Xanthanolides with antitumour activity from *Xanthium italicum*. *Z. Naturforsch. C* **2009**, *64*, 343–349. [[CrossRef](#)]
316. Sun, P.; Huo, J.; Kurtan, T.; Mandi, A.; Antus, S.; Tang, H.; Draeger, S.; Schulz, B.; Hussain, H.; Krohn, K.; et al. Structural and stereochemical studies of hydroxyanthraquinone derivatives from the endophytic fungus *Coniothyrium* sp. *Chirality* **2013**, *25*, 141–148. [[CrossRef](#)] [[PubMed](#)]
317. Yang, Y.; Yan, Y.M.; Wei, W.; Luo, J.; Zhang, L.S.; Zhou, X.J.; Wang, P.C.; Yang, Y.X.; Cheng, Y.X. Anthraquinone derivatives from *Rumex* plants and endophytic *Aspergillus fumigatus* and their effects on diabetic nephropathy. *Bioorg. Medicin. Chem. Lett.* **2013**, *23*, 3905–3909. [[CrossRef](#)] [[PubMed](#)]
318. Jayasuriya, H.; Koonchanok, N.M.; Geahlen, R.L.; McLaughlin, J.L.; Chang, C.J. Emodin, a protein tyrosine kinase inhibitor from *Polygonum cuspidatum*. *J. Nat. Prod.* **1992**, *55*, 696–698. [[CrossRef](#)] [[PubMed](#)]
319. Marinho, A.M.; Rodrigues-Filho, E.; Moitinho, M.D.; Santos, L.S. Biologically active polyketides produced by *Penicillium janthinellum* isolated as an endophytic fungus from fruits of *Melia azedarach*. *J. Braz. Chem. Soc.* **2005**, *16*, 280–283. [[CrossRef](#)]
320. Liu, F.; Cai, X.L.; Yang, H.; Xia, X.K.; Guo, Z.Y.; Yuan, J.; Li, M.F.; She, Z.G.; Lin, Y.C. The bioactive metabolites of the mangrove endophytic fungus *Talaromyces* sp. ZH-154 isolated from *Kandelia candel* (L.) Druce. *Planta Med.* **2010**, *76*, 185–189. [[CrossRef](#)]
321. Hawas, U.W.; El-Beih, A.A.; El-Halawany, A.M. Bioactive anthraquinones from endophytic fungus *Aspergillus versicolor* isolated from red sea algae. *Arch. Pharm. Res.* **2012**, *35*, 1749–1756. [[CrossRef](#)]
322. You, X.; Feng, S.; Luo, S.; Cong, D.; Yu, Z.; Yang, Z.; Zhang, J. Studies on a rhein-producing endophytic fungus isolated from *Rheum palmatum* L. *Fitoterapia* **2013**, *85*, 161–168. [[CrossRef](#)]
323. Zin, W.W.; Buttachon, S.; Dethoup, T.; Pereira, J.A.; Gales, L.; Inacio, A.; Costa, P.M.; Lee, M.; Sekeroglu, N.; Silva, A.M.; et al. Antibacterial and antibiofilm activities of the metabolites isolated from the culture of the mangrove-derived endophytic fungus *Eurotium chevalieri* KUFA 0006. *Phytochemistry* **2017**, *141*, 86–97. [[CrossRef](#)]
324. Vigneshwari, A.; Rakk, D.; Németh, A.; Kocsubé, S.; Kiss, N.; Csupor, D. Host metabolite producing endophytic fungi isolated from *Hypericum perforatum*. *PLoS ONE* **2019**, *14*, e0217060. [[CrossRef](#)]
325. Chomcheon, P.; Wiyakrutta, S.; Sriubolmas, N.; Ngamrojanavanich, N.; Mahidol, C.; Ruchirawat, S.; Kittakoop, P. Metabolites from the endophytic mitosporic *Dothideomycete* sp. LRUB20. *Phytochemistry* **2009**, *70*, 121–127. [[CrossRef](#)]
326. Kusari, S.; Lamshöft, M.; Zühlke, S.; Spittler, M. An endophytic fungus from *Hypericum perforatum* that produces hypericin. *J. Nat. Prod.* **2008**, *71*, 159–162. [[CrossRef](#)] [[PubMed](#)]
327. Kusari, S.; Zühlke, S.; Kosuth, J.; Cellárová, E.; Spittler, M. Light independent metabolomics of endophytic *Thielavia subthermophila* provides insight into microbial hypericin biosynthesis. *J. Nat. Prod.* **2009**, *72*, 1825–1835. [[CrossRef](#)]
328. Channabasava, R.; Govindappa, M. First report of anticancer agent, lapachol producing endophyte, *Aspergillus niger* of *Tabebuia argentea* and its in vitro cytotoxicity assays. *Bangladesh J. Pharmacol.* **2014**, *9*, 129–139. [[CrossRef](#)]

329. Sarang, H.; Rajani, P.; Vasanthakumari, M.M.; Kumara, P.M.; Siva, R.; Ravikanth, G.; Shaanker, R.U. An endophytic fungus, *Gibberella moniliformis* from *Lawsonia inermis* L. produces lawsone, an orange-red pigment. *Antonie Van Leeuwenhoek* **2017**, *110*, 853–862. [CrossRef]
330. Borges, W.D.; Pupo, M.T. Novel anthraquinone derivatives produced by *Phoma sorghina*, an endophyte found in association with the medicinal plant *Tithonia diversifolia* (Asteraceae). *J. Braz. Chem. Soc.* **2006**, *17*, 929–934. [CrossRef]
331. Liu, J.Y.; Song, Y.C.; Zhang, Z.; Wang, L.; Guo, Z.J.; Zou, W.X.; Tan, R.X. *Aspergillus fumigatus* CY018, an endophytic fungus in *Cynodon dactylon* as a versatile producer of new and bioactive metabolites. *J. Biotechnol.* **2004**, *114*, 279–287. [CrossRef] [PubMed]
332. Ge, H.M.; Song, Y.C.; Shan, C.Y.; Ye, Y.H.; Tan, R.X. New and cytotoxic anthraquinones from *Pleospora* sp. IFB-E006, an endophytic fungus in *Imperata cylindrical*. *Planta Med.* **2005**, *71*, 1063–1065. [CrossRef]
333. Wang, F.W.; Hou, Z.M.; Wang, C.R.; Li, P.; Shi, D.H. Bioactive metabolites from *Penicillium* sp., an endophytic fungus residing in *Hopea hainanensis*. *World J. Microbiol. Biotechnol.* **2008**, *24*, 2143–2147. [CrossRef]
334. Wu, S.H.; Chen, Y.W.; Qin, S.; Huang, R. A new spiroketal from *Aspergillus terreus*, an endophytic fungus in *Opuntia ficus-indica* Mill. *J. Basic Microbiol.* **2008**, *48*, 140–142. [CrossRef]
335. Zhang, Q.; Guo, W.J.; Fu, C.L.; Ma, S.; Zhu, M.Q. Chemical constituents from an endophyte, *Cercospora* sp. *Chem. Nat. Compd.* **2013**, *49*, 117–118. [CrossRef]
336. Law, K.K.; Chan, T.L.; Tam, S.W.; Shatin, N.T. Synthesis of pinselic acid and pinselin. *J. Org. Chem.* **1979**, *44*, 4452–4453. [CrossRef]
337. Song, X.Q.; Zhang, X.; Han, Q.J.; Li, X.B.; Li, G.; Li, R.J.; Jiao, Y.; Zhou, J.C.; Lou, H.X. Xanthone derivatives from *Aspergillus sydowii*, an endophytic fungus from the liverwort *Scapania ciliata* S. Lac and their immunosuppressive activities. *Phytochem. Lett.* **2013**, *6*, 318–321. [CrossRef]
338. Yang, H.Y.; Gao, Y.H.; Niu, D.Y.; Yang, L.Y.; Gao, X.M.; Du, G.; Hu, Q.F. Xanthone derivatives from the fermentation products of an endophytic fungus *Phomopsis* sp. *Fitoterapia* **2013**, *1*, 189–193. [CrossRef]
339. Yuan, L.; Huang, W.; Du, G.; Gao, X.; Yang, H.; Hu, Q.; Ma, Y. Isolation of Xanthenes from the Fermentation Products of the Endophytic Fungus of *Phomopsis amygdali*. *Chem. Nat. Compd.* **2015**, *51*, 460–463. [CrossRef]
340. Liu, H.; Chen, S.; Liu, W.; Liu, Y.; Huang, X.; She, Z. Polyketides with immunosuppressive activities from mangrove endophytic fungus *Penicillium* sp. ZJ-SY₂. *Drugs* **2016**, *14*, 217. [CrossRef]
341. Venkateswarulu, N.; Shameer, S.; Bramhachari, P.V.; Basha, S.T.; Nagaraju, C.; Vijaya, T. Isolation and characterization of plumbagin (5-hydroxyl-2-methylnaptalene-1, 4-dione) producing endophytic fungi *Cladosporium delicatulum* from endemic medicinal plants. *Biotechnol. Rep.* **2018**, *20*, e00282. [CrossRef]
342. Li, D.L.; Li, X.M.; Wang, B.G. Natural anthraquinone derivatives from a marine mangrove plant-derived endophytic fungus *Eurotium rubrum*, structural elucidation and DPPH radical scavenging activity. *J. Microbiol. Biotechnol.* **2009**, *19*, 675–680. [PubMed]
343. Du, F.Y.; Li, X.M.; Song, J.Y.; Li, C.S.; Wang, B.G. Anthraquinone derivatives and an orsellinic acid ester from the marine alga-derived endophytic fungus *Eurotium cristatum* EN-220. *Helv. Chim. Acta* **2014**, *97*, 973–978. [CrossRef]
344. Ren-Yi, G.; Lei, X.; Yi, K.; Iii-Ming, C.; Jian-Chun, Q.; Li, L.; Sheng-Xiang, Y.; Li-Chun, Z. Chaetominine, (+)-alantrypinone, questin, isorhodoptilometrin, and 4-hydroxybenzaldehyde produced by the endophytic fungus *Aspergillus* sp. YL-6 inhibit wheat (*Triticum aestivum*) and radish (*Raphanus sativus*) germination. *J. Plant Interact.* **2015**, *10*, 87–92. [CrossRef]
345. Xia, X.; Kim, S.; Bang, S.; Lee, H.J.; Liu, C.; Park, C.I.; Shim, S.H. Barceloneic acid C, a new polyketide from an endophytic fungus *Phoma* sp. JS752 and its antibacterial activities. *J. Antibiot.* **2015**, *68*, 139–141. [CrossRef]
346. Hammerschmidt, L.; Wray, V.; Lin, W.; Kamilova, E.; Proksch, P.; Aly, A.H. New styrylpyrones from the fungal endophyte *Penicillium glabrum* isolated from *Punica granatum*. *Phytochem. Lett.* **2012**, *5*, 600–603. [CrossRef]
347. Dzoyem, J.P.; Melong, R.; Tsamo, A.T.; Maffo, T.; Kapche, D.G.; Ngadjui, B.T.; McGaw, L.J.; Eloff, J.N. Cytotoxicity, antioxidant and antibacterial activity of four compounds produced by an endophytic fungus *Epicoccum nigrum* associated with *Entada abyssinica*. *Rev. Brasil. Farm* **2017**, *27*, 251–253. [CrossRef]
348. Movahhedini, N.; Albadry, M.; Hamann, M.T. Isolation and characterization of cytotoxic compounds from endophytes of an endangered American cactus, *Mammillaria hahniana*. *Planta Med.* **2014**, *80*, PD136. [CrossRef]
349. Mollaei, S.; Khanehbarndaz, O.; Gerami-Khashal, Z.; Ebadi, M. Molecular identification and phytochemical screening of endophytic fungi isolated from *Lithospermum officinale* L. roots: A new source of shikonin. *Phytochemistry* **2019**, *168*, 112–116. [CrossRef] [PubMed]
350. Ma, C.; Jiang, D.; Wei, X. Mutation breeding of *Emericella foeniculicola* TR21 for improved production of tanshinone IIA. *Proc. Biochem.* **2011**, *46*, 2059–2063. [CrossRef]
351. Ming, Q.L.; Han, T.; Li, W.; Zhang, Q.Y.; Zhang, H.; Zheng, C.J.; Huang, F.; Rahman, K.; Qin, L.P. Tanshinone IIA and tanshinone I production by *Trichoderma atroviride* D16, an endophytic fungus in *Salvia miltiorrhiza*. *Phytomedicine* **2012**, *19*, 330–333. [CrossRef] [PubMed]
352. Li, X.; Zhai, X.; Shu, Z.; Dong, R.; Ming, Q.; Qin, L.; Zheng, C. *Phoma glomerata* D14: An endophytic fungus from *Salvia miltiorrhiza* that produces salvianolic acid C. *Curr. Microbiol.* **2016**, *73*, 31–37. [CrossRef] [PubMed]
353. Lou, J.; Yu, R.; Wang, X.; Mao, Z.; Fu, L.; Liu, Y.; Zhou, L. Alternariol 9-methyl ether from the endophytic fungus *Alternaria* sp. Samif01 and its bioactivities. *Braz. J. Microbiol.* **2016**, *47*, 96–101. [CrossRef]
354. Lee, J.C.; Strobel, G.A.; Lobkovsky, E.; Clardy, J. Torreyanic acid: A selectively cytotoxic quinone dimer from the endophytic fungus *Pestalotiopsis microspora*. *J. Org. Chem.* **1996**, *61*, 3232–3233. [CrossRef]

355. Pizzorno, J.E.; Murray, M.T.; Joiner-Bey, H. *The Clinician's Handbook of Natural Medicine E-Book*, 3rd ed.; Elsevier Health Sciences: St Lois, MO, USA, 2016.
356. Jendželovská, Z.; Jendželovský, R.; Kuchárová, B.; Fedoročko, P. Hypericin in the light and in the dark: Two sides of the same coin. *Front. Plant Sci.* **2016**, *7*, 560. [[CrossRef](#)]
357. Furuya, T.; Kojima, H.; Katsuta, T. 3-Methylpurpurin and other anthraquinones from callus tissue of *Digitalis lanata*. *Phytochemistry* **1972**, *11*, 1073–1076. [[CrossRef](#)]
358. Fujii, N.; Yamashita, Y.; Arima, Y.; Nagashima, M.; Nakano, H. Induction of topoisomerase II-mediated DNA cleavage by the plant naphthoquinones plumbagin and shikonin. *Antimicrob. Agents Chemother.* **1992**, *36*, 2589–2594. [[CrossRef](#)] [[PubMed](#)]
359. Checker, R.; Patwardhan, R.S.; Sharma, D.; Sandur, S.K. Chemopreventive and anticancer effects of plumbagin: Novel mechanism (s) via modulation of cellular redox. In *Role of Nutraceuticals in Cancer Chemosensitization*; Bharti, A.C., Aggarwal, B.B., Eds.; Academic Press; Elsevier: San Diego, CA, USA, 2018; pp. 325–341. ISSN 2468-3183.
360. Cao, Y.Y.; Yu, J.; Liu, T.T.; Yang, K.X.; Yang, L.Y.; Chen, Q.; Shi, F.; Hao, J.J.; Cai, Y.; Wang, M.R.; et al. Plumbagin inhibits the proliferation and survival of esophageal cancer cells by blocking STAT3-PLK1-AKT signaling. *Cell Death Dis.* **2018**, *9*, 1–13. [[CrossRef](#)] [[PubMed](#)]
361. Gong, K.; Li, W. Shikonin, a Chinese plant-derived naphthoquinone, induces apoptosis in hepatocellular carcinoma cells through reactive oxygen species: A potential new treatment for hepatocellular carcinoma. *Free Rad. Biol. Med.* **2011**, *51*, 2259–2271. [[CrossRef](#)] [[PubMed](#)]
362. Sheng, X.; Wang, M.; Lu, M.; Xi, B.; Sheng, H.; Zang, Y.Q. Rhein ameliorates fatty liver disease through negative energy balance, hepatic lipogenic regulation, and immunomodulation in diet-induced obese mice. *Am. J. Physiol. Endocrinol. Metab.* **2011**, *300*, 886–893. [[CrossRef](#)]
363. Mendes, A.F.; Caramona, M.M.; de Carvalho, A.P.; Lopes, M.C. Diacerhein and rhein prevent interleukin-1beta-induced nuclear factor-kappaB activation by inhibiting the degradation of inhibitor kappaB-alpha. *Pharmacol. Toxicol.* **2002**, *91*, 22–28. [[CrossRef](#)]
364. Sun, H.; Luo, G.; Chen, D.; Xiang, Z. A comprehensive and system review for the pharmacological mechanism of action of rhein, an active anthraquinone ingredient. *Front. Pharmacol.* **2016**, *7*, 247. [[CrossRef](#)]
365. Fernand, V.E.; Losso, J.N.; Truax, R.E.; Villar, E.E.; Bwambok, D.K.; Fakayode, S.O.; Lowry, M.; Warner, I.M. Rhein inhibits angiogenesis and the viability of hormone-dependent and -independent cancer cells under normoxic or hypoxic conditions in vitro. *Chem. Biol. Interact.* **2011**, *192*, 220–232. [[CrossRef](#)]
366. Jiang, Z.; Gao, W.; Huang, L. Tanshinones, critical pharmacological components in *Salvia miltiorrhiza*. *Front. Pharmacol.* **2019**, *10*, 202. [[CrossRef](#)]
367. Ming, Q.; Su, C.; Zheng, C.; Jia, M.; Zhang, Q.; Zhang, H.; Rahman, K.; Han, T.; Qin, L. Elicitors from the endophytic fungus *Trichoderma atroviride* promote *Salvia miltiorrhiza* hairy root growth and tanshinone biosynthesis. *J. Experiment. Bot.* **2013**, *64*, 5687–5694. [[CrossRef](#)]
368. Zhai, X.; Luo, D.; Li, X.; Han, T.; Jia, M.; Kong, Z.; Ji, J.; Rahman, K.; Qin, L.; Zheng, C. Endophyte *Chaetomium globosum* D38 promotes bioactive constituents accumulation and root production in *Salvia miltiorrhiza*. *Front. Microbiol.* **2018**, *8*, 2694. [[CrossRef](#)]
369. Schwarz, M.; Köpcke, B.; Weber, R.W.; Sterner, O.; Anke, H. 3-Hydroxypropionic acid as a nematocidal principle in endophytic fungi. *Phytochemistry* **2004**, *65*, 2239–2245. [[CrossRef](#)] [[PubMed](#)]
370. Chomcheon, P.; Wiyakrutta, S.; Sriubolmas, N.; Ngamrojanavanich, N.; Isarangkul, D.; Kittakoop, P. 3-Nitropropionic acid (3-NPA), a potent antimycobacterial agent from endophytic fungi: Is 3-NPA in some plants produced by endophytes? *J. Nat. Prod.* **2005**, *68*, 1103–1105. [[CrossRef](#)] [[PubMed](#)]
371. Flores, A.C.; Pamphile, J.A.; Sarragiotto, M.H.; Clemente, E. Production of 3-nitropropionic acid by endophytic fungus *Phomopsis longicolla* isolated from *Trichilia elegans* A. JUSS and evaluation of biological activity. *World J. Microbiol. Biotechnol.* **2013**, *29*, 923–932. [[CrossRef](#)] [[PubMed](#)]
372. Saxena, S.; Meshram, V.; Kapoor, N. *Muscodor tigerii* sp. nov.-Volatile antibiotic producing endophytic fungus from the Northeastern Himalayas. *Ann. Microbiol.* **2015**, *65*, 47–57. [[CrossRef](#)]
373. Gu, X.J.; Ren, K.; Yao, N.; Yan, S.; Zhao, J.F.; Jiang, X.Y.; Lian, Q. Chemical constituents from endophytic fungus *Plectosphaerella cucumerina* YCTA2Z1 of *Cynanchum auriculatum*. *Chin. Herb. Med.* **2018**, *10*, 95–98. [[CrossRef](#)]
374. Kamat, S.; Kumari, M.; Taritla, S.; Jayabaskaran, C. Endophytic fungi of marine alga from Konkan coast, India—A rich source of bioactive material. *Front. Mar. Sci.* **2020**, *7*, 31. [[CrossRef](#)]
375. Guo, B.; Dai, J.R.; Ng, S.; Huang, Y.; Leong, C.; Ong, W.; Carte, B.K. Cytonic acids A and B: Novel tridepside inhibitors of hCMV protease from the endophytic fungus *Cytospora* species. *J. Nat. Prod.* **2000**, *63*, 602–604. [[CrossRef](#)]
376. Zhao, J.; Fu, Y.; Luo, M.; Zu, Y.; Wang, W.; Zhao, C.; Gu, C. Endophytic fungi from pigeon pea (*Cajanus cajan* (L.) Millsp.) produce antioxidant cajanin stilbene acid. *J. Agric. Food Chem.* **2012**, *60*, 4314–4319. [[CrossRef](#)]
377. Chen, X.; Sang, X.; Li, S.; Zhang, S.; Bai, L. Studies on a chlorogenic acid-producing endophytic fungi isolated from *Eucommia ulmoides* Oliver. *J. Ind. Microbiol. Biotechnol.* **2010**, *37*, 447–454. [[CrossRef](#)]
378. Kaul, S.; Wani, M.; Dhar, K.L.; Dhar, M.K. Production and GC-MS trace analysis of methyl eugenol from endophytic isolate of *Alternaria* from rose. *Ann. Microbiol.* **2008**, *58*, 443. [[CrossRef](#)]
379. Cheng, M.J.; Wu, M.D.; Chen, J.J.; Cheng, Y.C.; Hsieh, M.T.; Hsieh, S.Y.; Yuan, G.F.; Su, Y.S. Secondary metabolites from the endophytic fungus *Annulohyphoxylon stygium* BCRC 34024. *Chem. Nat. Compd.* **2014**, *50*, 237–241. [[CrossRef](#)]

380. Faisal, M.P.; Prasad, L.A. Potential source of methyl-eugenol from secondary metabolite of *Rhizopus oryzae* 6975. *Int. J. Appl. Biol. Pharm. Technol.* **2016**, *7*, 187–192.
381. Tanapichatsakul, C.; Khruengsai, S.; Monggoot, S.; Pripdeevech, P. Production of eugenol from fungal endophytes *Neopestalotiopsis* sp. and *Diaporthe* sp. isolated from *Cinnamomum loureiroi* leaves. *PeerJ* **2019**, *7*, e6427. [[CrossRef](#)] [[PubMed](#)]
382. Kaul, S.; Ahmed, M.; Zargar, K.; Sharma, P.; Dhar, M.K. Prospecting endophytic fungal assemblage of *Digitalis lanata* Ehrh. (foxglove) as a novel source of digoxin: A cardiac glycoside. *3 Biotech* **2013**, *3*, 335–340. [[CrossRef](#)]
383. Mir, R.A.; Kaushik, S.P.; Chowdery, R.A.; Anuradha, M. Elicitation of forskolin in cultures of *Rhizactonia bataticola*-a phytochemical synthesizing endophytic fungi. *Int. J. Pharm. Pharma. Sci.* **2015**, *7*, 185–189.
384. Seger, C.; Godejohann, M.; Tseng, L.H.; Spraul, M.; Girtler, A.; Sturm, S.; Stuppner, H. LC-DAD-MS/SPE-NMR hyphenation. A tool for the analysis of pharmaceutically used plant extracts: Identification of isobaric irid glycoside regioisomers from *Harpagophytum procumbens*. *Anal. Chem.* **2005**, *77*, 878–885. [[CrossRef](#)]
385. Shen, Z.Y.; Zhu, B.; Zhang, Q.L.; Qin, L.P. Isolation and identification of endophytic fungi producing harpagoside and harpagide from *Scrophularia ningpoensis*. *China J. Chin. Mat. Med.* **2019**, *44*, 2046–2050.
386. Nicoletti, R.; Ferranti, P.; Caira, S.; Misso, G.; Castellano, M.; Di Lorenzo, G.; Caraglia, M. Myrtycommulone production by a strain of *Neofusicoccum australe* endophytic in myrtle (*Myrtus communis*). *World J. Microbiol. Biotechnol.* **2014**, *30*, 1047–1052. [[CrossRef](#)]
387. Ruangrunsi, N.; Wongpanich, V.; Tantivatana, P.; Cowe, H.J.; Cox, P.J.; Funayama, S.; Cordell, G.A. Traditional medicinal plants of Thailand, V. Ancistrocladine, a new naphthalene-isoquinoline alkaloid from *Ancistrocladus tectorius*. *J. Nat. Prod.* **1985**, *48*, 529–535. [[CrossRef](#)]
388. Daisy, B.H.; Strobel, G.A.; Castillo, U.; Ezra, D.; Sears, J.; Weaver, D.K.; Runyon, J.B. Naphthalene, an insect repellent, is produced by *Muscodor vitigenus*, a novel endophytic fungus. *Microbiology* **2002**, *148*, 3737–3741. [[CrossRef](#)] [[PubMed](#)]
389. Dai, J.; Krohn, K.; Draeger, S.; Schulz, B. New naphthalene-chroman coupling products from the endophytic fungus, *Nodulisporium* sp. from *Erica arborea*. *Eur. J. Org. Chem.* **2009**, *2009*, 1564–1569. [[CrossRef](#)]
390. Gond, S.K.; Mishra, A.; Sharma, V.K.; Verma, S.K.; Kharwar, R.N. Isolation and characterization of antibacterial naphthalene derivative from *Phoma herbarum*, an endophytic fungus of *Aegle marmelos*. *Curr. Sci.* **2013**, *105*, 167–169.
391. Shi, J.; Zeng, Q.; Liu, Y.; Pan, Z. *Alternaria* sp. MG1, a resveratrol-producing fungus: Isolation, identification, and optimal cultivation conditions for resveratrol production. *Appl. Microbiol. Biotechnol.* **2012**, *95*, 369–379. [[CrossRef](#)] [[PubMed](#)]
392. Cui, J.; Guo, T.; Chao, J.; Wang, M.; Wang, J. Potential of the endophytic fungus *Phialocephala fortinii* Rac56 found in *Rhodiola* plants to produce salidroside and p-tyrosol. *Molecules* **2016**, *21*, 502. [[CrossRef](#)]
393. Xu, J.; Luo, X.; Zhong, W.; Zhang, J.; Tan, R. Characterization of volatile constituents from an endophytic *Aspergillus fumigatus* strain. *J. Chem. Pharm. Res.* **2014**, *6*, 893–897.
394. Liang, L.; Luo, M.; Fu, Y.; Zu, Y.; Wang, W.; Gu, C.; Zhao, C.; Li, C.; Efferth, T. Cajaninstilbene acid (CSA) exerts cytoprotective effects against oxidative stress through the Nrf2-dependent antioxidant pathway. *Toxicol. Lett.* **2013**, *219*, 254–261. [[CrossRef](#)]
395. Huang, M.Y.; Lin, J.; Lu, K.; Xu, H.G.; Geng, Z.Z.; Sun, P.H.; Chen, W.M. Anti-inflammatory effects of cajaninstilbene acid and its derivatives. *J. Agric. Food Chem.* **2016**, *64*, 2893–2900. [[CrossRef](#)]
396. Wang, L.S.; Tao, X.; Liu, X.M.; Zhou, Y.F.; Zhang, M.D.; Liao, Y.H.; Pan, R.L.; Chang, Q. Cajaninstilbene acid ameliorates cognitive impairment induced by intrahippocampal injection of amyloid- β 1-42 oligomers. *Front. Pharmacol.* **2019**, *10*, 1084. [[CrossRef](#)]
397. Ren, Y.; Ribas, H.T.; Heath, K.; Wu, S.; Ren, J.; Shriwas, P.; Chen, X.; Johnson, M.E.; Cheng, X.; Burdette, J.E.; et al. Na⁺/K⁺-ATPase-targeted cytotoxicity of (+)-digoxin and several semisynthetic derivatives. *J. Nat. Prod.* **2020**, *83*, 638–648. [[CrossRef](#)]
398. Pateraki, I.; Andersen-Ranberg, J.; Jensen, N.B.; Wubshet, S.G.; Heskes, A.M.; Forman, V.; Hallström, B.; Hamberger, B.; Motawia, M.S.; Olsen, C.E.; et al. Total biosynthesis of the cyclic AMP booster forskolin from *Coleus forskohlii*. *Elife* **2017**, *6*, e23001. [[CrossRef](#)] [[PubMed](#)]
399. Laurenza, A.; Sutkowski, E.M.; Seamon, K.B. Forskolin: A specific stimulator of adenylyl cyclase or a diterpene with multiple sites of action? *Trends Pharmacol. Sci.* **1989**, *10*, 442–447. [[CrossRef](#)]
400. Chiang, H.M.; Chen, H.C.; Wu, C.S.; Wu, P.Y.; Wen, K.C. *Rhodiola* plants: Chemistry and biological activity. *J. Food Drug Anal.* **2015**, *23*, 359–369. [[CrossRef](#)]
401. Lee, S.Y.; Shi, L.S.; Chu, H.; Li, M.H.; Ho, C.W.; Lai, F.Y.; Huang, C.Y.; Chang, T.C. *Rhodiola crenulata* and its bioactive components, salidroside and tyrosol, reverse the hypoxia-induced reduction of plasma-membrane-associated Na, K-ATPase expression via inhibition of ROS-AMPK-PKC ξ pathway. *Evid. Based Complement. Alternat. Med.* **2013**, *2013*, 1–15.
402. Zhong, Z.; Han, J.; Zhang, J.; Xiao, Q.; Hu, J.; Chen, L. Pharmacological activities, mechanisms of action, and safety of salidroside in the central nervous system. *Drug Des. Devel. Ther.* **2018**, *12*, 1479. [[CrossRef](#)] [[PubMed](#)]
403. Potterat, O.; Hamburger, M. Concepts and technologies for tracking bioactive compounds in natural product extracts: Generation of libraries, and hyphenation of analytical processes with bioassays. *Nat. Prod. Rep.* **2013**, *30*, 546–564. [[CrossRef](#)] [[PubMed](#)]
404. Kharwar, R.N.; Sharma, V.K.; Mishra, A.; Kumar, J.; Singh, D.K.; Verma, S.K.; Gond, S.K.; Kumar, A.; Kaushik, N.; Revuru, B.; et al. Harnessing the phytotherapeutic treasure troves of the ancient medicinal plant *Azadirachta indica* (Neem) and associated endophytic microorganisms. *Planta Med.* **2020**, *86*, 906–940. [[CrossRef](#)] [[PubMed](#)]
405. Hillman, E.T.; Readnour, L.R.; Solomon, K.V. Exploiting the natural product potential of fungi with integrated-omics and synthetic biology approaches. *Curr. Opin. Syst. Biol.* **2017**, *5*, 50–56. [[CrossRef](#)]

-
406. Hautbergue, T.; Jamin, E.L.; Debrauwer, L.; Puel, O.; Oswald, I.P. From genomics to metabolomics, moving toward an integrated strategy for the discovery of fungal secondary metabolites. *Nat. Prod. Rep.* **2018**, *35*, 147–173. [[CrossRef](#)]
 407. Swift, C.L.; Podolsky, I.A.; Lankiewicz, T.S.; Seppälä, S.; O'Malley, M.A. Linking 'omics' to function unlocks the biotech potential of non-model fungi. *Curr. Opin. Syst. Biol.* **2019**, *14*, 9–17.
 408. Romano, S.; Jackson, S.A.; Patry, S.; Dobson, A.D. Extending the “one strain many compounds” (OSMAC) principle to marine microorganisms. *Mar. Drugs* **2018**, *16*, 244. [[CrossRef](#)] [[PubMed](#)]
 409. Pan, R.; Bai, X.; Chen, J.; Zhang, H.; Wang, H. Exploring structural diversity of microbe secondary metabolites using OSMAC strategy: A literature review. *Front. Microbiol.* **2019**, *10*, 294. [[CrossRef](#)] [[PubMed](#)]
 410. Ariantari, N.P.; Daletos, G.; Mándi, A.; Kurtán, T.; Müller, W.E.; Lin, W.; Ancheeva, E.; Proksch, P. Expanding the chemical diversity of an endophytic fungus *Bulgaria inquinans*, an ascomycete associated with mistletoe, through an OSMAC approach. *RSC Adv.* **2019**, *9*, 25119–25132. [[CrossRef](#)]
 411. Amirkia, V.; Heinrich, M. Natural products and drug discovery: A survey of stakeholders in industry and academia. *Front. Pharmacol.* **2015**, *6*, 237. [[CrossRef](#)] [[PubMed](#)]
 412. Jiang, D.; Zhu, W.; Wang, Y.; Sun, C.; Zhang, K.Q.; Yang, J. Molecular tools for functional genomics in filamentous fungi: Recent advances and new strategies. *Biotechnol. Adv.* **2013**, *31*, 1562–1574. [[CrossRef](#)]
 413. Singh, B.N.; Upreti, D.K.; Gupta, V.K.; Dai, X.F.; Jiang, Y. Endolichenic fungi: A hidden reservoir of next generation biopharmaceuticals. *Trends Biotechnol.* **2017**, *35*, 808–813. [[CrossRef](#)]