

Review

Linking Endophytic Fungi to Medicinal Plants Therapeutic Activity. A Case Study on Asteraceae

Gianluca Caruso ¹, Magdi T. Abdelhamid ², Andrzej Kalisz ³ and Agnieszka Sekara ^{3,*}

¹ Department of Agricultural Sciences, University of Naples Federico II, 80055 Portici (Naples), Italy; gcaruso@unina.it

² Botany Department, National Research Centre, Cairo 12622, Egypt; mt.abdelhamid@nrc.sci.eg

³ Department of Horticulture, Faculty of Biotechnology and Horticulture, University of Agriculture, 31-120 Krakow, Poland; andrzej.kalisz@urk.edu.pl

* Correspondence: agnieszka.sekara@urk.edu.pl

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Abstract: Endophytes are isolated from every plant species investigated to date, so the metabolome coevolution has been affecting the plants' (microbiota) ethnobotanic, especially therapeutic, usage. Asteraceae fulfill the rationale for plant selection to isolate endophytes since most of the species of this family have a long tradition of healing usage, confirmed by modern pharmacognosy. The present review compiles recent references on the endophyte–Asteraceae spp. interactions, targeting the secondary metabolites profile as created by both members of this biological system. Endophyte fungi associated with Asteraceae have been collected globally, however, dominant taxa that produce bioactive compounds were specific for the plant populations of different geographic origins. Endophytic fungi richness within the host plant and the biological activity were positively associated. Moreover, the pharmacological action was linked to the plant part, so differential forms of biological interactions in roots, stem, leaves, inflorescences were developed between endophytic fungi and host plants. The comparative analysis of the Asteraceae host and/or fungal endophyte therapeutic activity showed similarities that need a future explanation on the metabolome level.

Keywords: compositae; fungi; herbs; secondary metabolites; symbiosis

1. Introduction

Each plant coexists with microorganisms residing within tissues and producing their metabolites, which are defined as endophytes if their occurrence does not cause apparent injuries [1,2]. Wilson [3] defined “endophytes” (from Greek endon—within; and phyton—plant) as microorganisms, commonly fungi and bacteria, spending their life cycle inter- and/or intra-cell space of the tissues of host plants, which do not show any symptoms of disease. Endophytes were isolated from plants belonging to all taxa investigated to date, occurring in all the world's ecosystems. In recent years, there has been an increased interest in explaining the endophytes/host plant cross-talk because the effects of these relationships could be beneficial to humans [1,4–6]. Host plants abide endophytes due to symbiotic relationships, profitable for microbes due to the availability of habitat and nutrients in the plant, while plants acquire a wide spectrum of microbial metabolites, including vitamins, hormones, and antibiotics [7,8]. Endophyte–host relationships can be so close, that microbes can even biosynthesize the same chemical compounds as the host, as myrtoaccumulones from *Myrtus communis*, camptothecin from *Camptotheca acuminata*, paclitaxel from *Taxus brevifolia*, or deoxypodophyllotoxin from *Juniperus communis* for better adaptation to the microenvironment of plant tissues [7,9–13]. It is an unresolved hypothesis that the production of secondary metabolites in plants is not achieved only by endophytes but arises from concomitant plant and fungal biosynthesis [13]. Endophytes occupy a unique ecological

niche, their relationship with a host plant a balance between mutualistic, parasitic, or commensal symbiosis, which is largely controlled via chemicals. That is the reason why endophytes produce highly specific metabolites [14]. Indeed, these microorganisms are being increasingly investigated as they play an important role in natural product discovery, especially when the source plant is used for medicinal purposes. In the latter respect, the healing action can be the result not only of the host plant metabolome but also the microorganism-derived active compounds and their interactions [4]. Moreover, organic extracts obtained from isolated endophytes show a wide spectrum of biological action and may be applied as antidiabetic, antimicrobial, antiviral, larvicidal, antimalarial, cytotoxic, and plant growth promoters [15,16]. The problem is that some endophyte genes responsible for secondary metabolite biosynthesis were found to be significantly expressed in planta but silent in vitro cultures. Plant and coexisting microbial signal molecules are required to induce particular pathways of endophyte metabolism leading to a balance of sexual to asexual reproduction and biochemical profile modification as well [17–20]. Moreover, the secondary metabolites are energy-consuming compounds, so endophytes can increase/decrease their production depending on specific needs, like competition with the other microorganisms or host plant communication and protection [9,21–23]. However, some fungal endophytes were shown to produce the desired compounds without a host plant association. Sustainable synthesis of tanshinone IIA and taxol by the axenic culture of endophytic fungi have been reported by Ma et al. [24] and Zhao et al. [25]. Karuppusamy [26] presented the possible origin of secondary metabolites in plant-endophyte systems, namely (i) parallel coevolution of plants and their microbiota possessing pathways to produce bioactive compounds; (ii) horizontal gene transfer between plants and microbes during their coevolution; (iii) plants or endophytic fungi synthesize and transfer metabolites to each other. Recent studies provided strong indications that endophytic fungi dispose host-independent machinery for secondary metabolite production [27–29]. Metabolites of fungal endophytes which were isolated from medicinal plants possess diverse and unique structural groups. That is the reason why they are good sources of novel secondary metabolic products contributing to the therapeutic activity [30–32]. Among medicinal plants, the members of Asteraceae family have been reported to be a source of natural remedies in all traditional medicine systems since their secondary metabolites exhibit strong antioxidant, antibacterial or anti-inflammatory activities [33].

The production of bioactive secondary metabolites by endophytic fungi colonizing medicinal plants has been largely ignored. The main idea of this review is that the Asteraceae evolutionary success is the effect of interaction between the host plant and fungal endophytic microbiota. We focused on determining the possible contribution of fungal biosynthesis to the secondary metabolome of Asteraceae, as a leading family of medicinal plants, to present the additional explanation for the distribution of bioactive compounds, including alkaloids, cardiac glycosides, and anthraquinones in the plant kingdom. We reviewed the available literature to assess therapeutic activity that had been reported previously from medicinal plants of the Asteraceae family that may likewise originate from endophytic fungi that coexist with these plants. We tried to estimate if the plants' taxonomic affinity affects the endophytic microbiome biodiversity and metabolic pathways.

2. Asteraceae Ecology and Biochemistry

The family Asteraceae (Compositae) is the largest and most cosmopolitan group of angiosperms covering 32,913 accepted species, grouped in 1911 genera and 13 subfamilies [34]. Asteraceae comprise more than 40 economically important crops, including food crops (*Lactuca sativa*, *Cichorium* spp., *Cynara scolymus*, *Smallanthus sonchifolius*, and *Helianthus tuberosus*), oil crops (*Helianthus annuus*, *Carthamus tinctorius*), medicinal and aromatic plants (*Matricaria chamomilla*, *Chamaemelum nobile*, *Calendula* spp., *Echinacea* spp., and *Artemisia* spp.), ornamentals (*Chrysanthemum* spp., *Gerbera* spp., *Dendranthema* spp., *Argyranthemum* spp., *Dahlia* spp., *Tagetes* spp., and *Zinnia* spp.), and nectar producers (*Centaurea* spp., *H. annuus*, and *Solidago* spp.) [35]. Species of this family represent a great variation regarding the habit: annual, perennial, herbs, shrubs, vines, trees, epiphytes; with the inflorescence composed of one to more than a thousand florets; and chromosome numbers range from $n = 2$ to $n = 114$ [36]. The Asteraceae

store energy in the form of inulin [37], they can produce acetylenes, alcohols, alkaloids, organic acids, pentacyclic triterpenes, sesquiterpene lactones, and tannins [38–40]. They are globally distributed although most are native to temperate climatic zones, the Mediterranean zone, or higher-elevation, cooler regions of the tropics [41]. The unique success of Asteraceae in worldwide distribution has been attributed to many factors, including diversity of secondary metabolites that improve overall fitness, a highly specialized inflorescence that maximizes fertilization, and a morphology promoting outcrossing [42]. Many species of the Asteraceae family have been used as medicinal plants, although the secondary metabolites responsible for the pharmacological efficiency were not always defined. The chemical diversity of bioactive compounds and pathways of their biosynthesis is dependent on a broad spectrum of biotic and abiotic factors and their interactions. Sometimes the benefits of plant-derived pharmacological products are controversial despite standard chemical composition with the use of commonly accepted pharmacopeia's methods [43]. Numerous papers have described the pharmacological activity and chemical constituents isolated from plants of the Asteraceae, covering polyphenols, sesquiterpenes, organic and fatty acids which have been associated with the successful treatment of cardiovascular diseases, cancer, microbial and viral infections, inflammation, and other diseases [43]. Most of the Asteraceae taxa, like *Artemisia*, are well known for their resistance to herbivores, bacterial and fungal pathogens [44]. Secondary metabolites are chemicals of a very diversified structure, not fundamental in the plant metabolism, but crucial for protection against pathogens and herbivores [45]. With the use of principal component analysis, Alvarenga et al. [46] showed the relationships between chemical composition and botanical classification of Asteraceae family, based on a huge group of 4000 species and 11 main chemical classes of secondary metabolites. *Barnadesieae* tribe revealed an anomalous position owing to the poor diversity of its secondary metabolites, particularly flavonoids. *Liabeae* and *Vernonieae* tribes were localized closely because of similar lactone composition, while *Asteridae* was separated because of monoterpenes, diterpenes, sesquiterpenes content. Moreover, the correlation matrix of Asteraceae secondary metabolites showed that benzofuranes and acetophenones, as well as diterpenes and phenylpropanoids, were highly correlated with each other [46]. The role of fungal endophytes in Asteraceae's evolutionary success has been recently recognized by the scientific community, although there is still a need for complex investigations in this area. The multifarious metabolome of Asteraceae is a dynamic patchwork of chemicals synthesized solely by the plant, by the microbial inhibiting the host species, or by both elements of this ecological system.

3. Fungal Endophytes Associated with Asteraceae—Biodiversity, and Ecology

The high diversity of endophytes indicates their multiple and variable relations with the host plants and ecological functions. The widest research program to find endophytes in medicinal Asteraceae has been performed in countries which are localized in the most important biodiversity hotspots, like Brazil, China, the Mediterranean region, Iran, or Thailand [47]. In Brazil, like the other South American countries, medicinal plants have been used as a traditional, cheap, and easily available alternative to drugs. Only a few tropical herbs were investigated with respect to endophytic fungal communities with bioactivity [48–50]. Another region of Asteraceae collection as host plants for fungal endophytes is the Panxi plateau in China [51] with xerothermic climate, diversified soil, and landscape conditions contributing to the high biodiversity in the area, concerning also medicinal plants having a long history of application by local communities [52]. The global screening reflected in the present review showed minimal knowledge on Asteraceae in this respect (Figure 1).

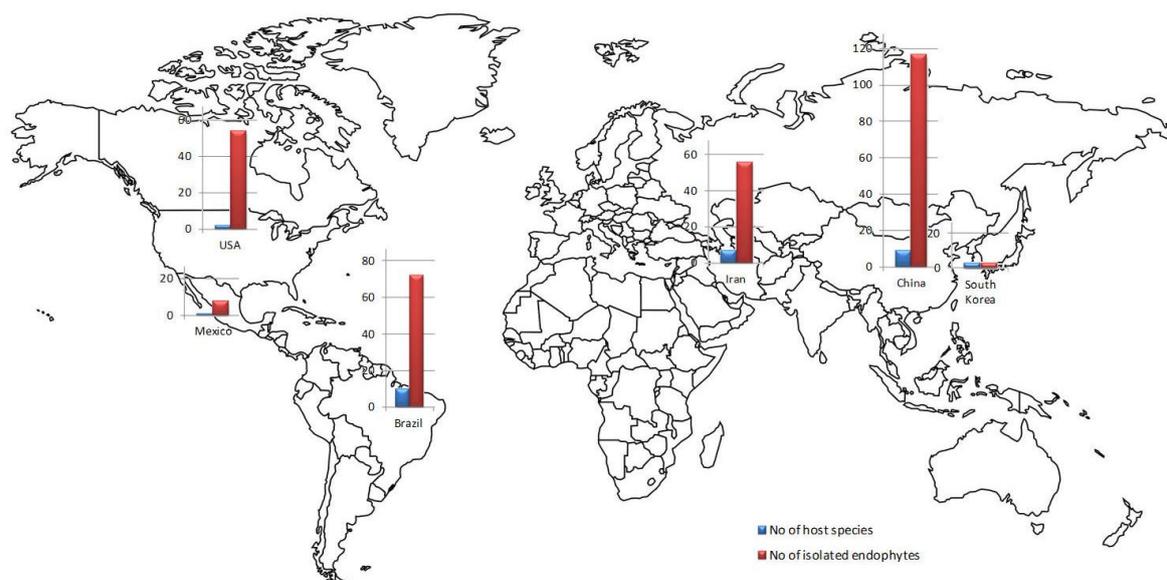


Figure 1. The Asteraceae hosts and endophyte fungi isolated from them in chosen countries (based on the references cited in this review).

Despite the high diversity and abundance of the Asteraceae worldwide, fungal endophytes associated with the plants of this family represented common or cosmopolitan species [53]. In light of the present review, about 23% of fungi taxa isolated from Asteraceae were associated with one host (Figure 2). They were mentioned in the footnote of Figure 2 as “The others”. The most abundant fungi genera, *Colletotrichum*, *Alternaria*, *Penicillium*, etc., were ubiquitous and isolated from most plant species and environments [10].

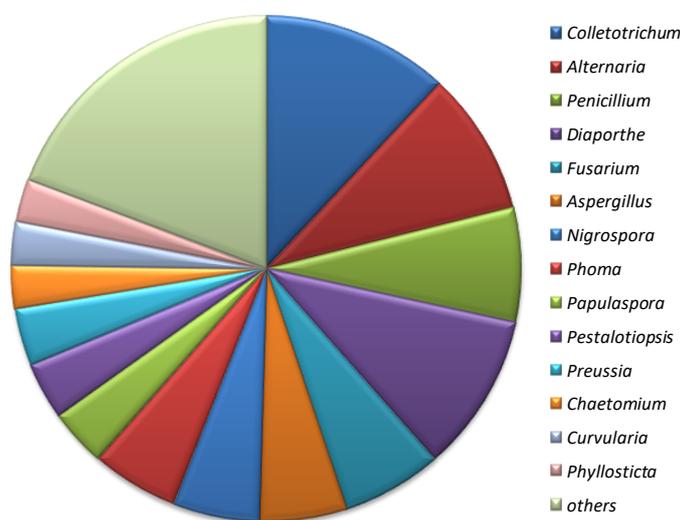


Figure 2. The frequency of isolation of endophytes (%) from Asteraceae host plants. The others: *Acremonium*, *Ampelomyces*, *Bipolaris*, *Botryosphaeria*, *Botrytis*, *Calonectria*, *Cercospora*, *Coniochaeta*, *Cylindrocarpon*, *Epicoccum*, *Exserohilum*, *Memmoniella*, *Paecilomyces*, *Periconia*, *Podospora*, *Pezicula*, *Pyrenophora*, *Scopulariopsis*, *Seiridium*, *Trichoderma*, *Xylaria* (based on references cited in this review).

To date, most of the research was focused on the overall spectrum of endophytes of the particular host plant or the particular endophyte taxon isolated from a wide range of host plants. To validate, Rodríguez–Rodríguez et al. [49] compared microorganism diversity and abundance in *Aster grisebachii* (synonym of *Neja marginata*), *Erigeron bellidiastroides*, *Erigeron cuneifolius*, *Pectis juniperina*, and *Sachsia*

polycephala (Asteraceae), native to Cuba, collected in an area with a low-in-nutrients, acid, sandy soil with alternating dry, and rainy seasons. The colonization rate was higher than 50% in both the dry and rainy period for all species which is typical for changing and stressful ecosystems, with strong competition for soil resources. *Pestalotiopsis* spp. were isolated as dominant from the different medicinal plants originated to tropical and subtropical climatic zones [54]. *Preussia* spp. isolated from leaves of medicinal plants *Baccharis trimera* (Asteraceae) and *Stryphnodendron adstringens* (Fabaceae) are native to Brazilian savannah [55]. A study performed by Hatamzadeh et al. [56], on native Asteraceae medicinal plants of Iran, allowed to isolate 241 endophyte species from *Cota segetalis* (syn. *Anthemis altissima*), 163 from *Achillea millefolium*, 121 from *Anthemis triumfettii* (synonym of *Cota triumfettii* subsp. *triumfettii*), 132 from *Cichorium intybus*, 90 from *Achillea filipendulina*, and 59 from *M. chamomilla*. A few endophytic fungi such as *Acremonium sclerotigenum*, *Alternaria burnsii*, *Bjerkandera adusta*, *Colletotrichum tanacetii*, *Epicoccum nigrum*, *Fusarium acuminatum*, *Paraphoma chrysanthemicola*, *Plectosphaerella cucumerina*, and *Stemphylium amaranthi* were isolated from all host species [56], most of them colonizing the stem of the plant. Although Cheng et al. [57] concluded that the structure of the endophytic communities differed within plant tissues and habitats, similarities in the taxa of the endophytic fungi were rarely observed at the phylum order or even the host plant family level. Endophyte communities were characterized by ecological variation, different host preference, tissue specificity, spatial heterogeneity, and seasonal changes in terms of composition and quantity of fungal endophytic strains which can affect medicinal plant biochemical composition [58]. Investigations of endophytes coexisting with *Ageratina altissima* showed that the fungal microbiome was driven by host individual and geographic location. Moreover, the endophyte community of a single host collected in the urban zone was less abundant compared to the forest probably due to human disturbance and spatial isolation [59]. The expansion of the invasive species *Ageratina adenophora* was studied concerning the distribution of endophytes in tissues in surrounding environments [60–62]. The enrichment of *A. adenophora* endophytes was root tissue-specific, moreover, fungi rarely grew systemically within the plant. The roots were the habitat of *Fusarium*, the stems of *Allophoma*, the mature leaves of *Colletotrichum*, and *Diaporthe*. Additionally, some fungi might migrate tissue-to-tissue via the vascular system of the shoot, and this was the way airborne fungi infected roots, and soilborne fungi, shoots, and leaves. Leaf endophytes showed more fluctuations in the number of taxa than those in roots and stems, because of the stronger pressure of environmental factors [62]. Presented studies indicated that fungal endophyte communities varied based on host genotype or even specimen, plant tissue, growth stage, and growth conditions. The research referenced in this review were focused on the taxonomical analysis of endophytes collected in a particular area from different Asteraceae taxa, or one species, or from different tissues of that species. Another main field of investigation were secondary metabolites produced by endophytes in situ or in vitro. Table 1 summarizes the biological action of Asteraceae plant extracts and endophytes isolated from them. The evident similarities indicate that the therapeutic activity of Asteraceae plants used traditionally as herbal remedies can also be referred to associated fungal endophytes. Almost all internal symbiotic fungi showed in vitro similar activity to those of their host plant extract. However, the present review of the literature published during the last twenty years showed insufficient experimental evidence to describe the endophyte/host plant interactions on the metabolome level, so the biosynthetic pathway might be differently regulated in the fungus and the host plant.

Table 1. Endophytes isolated from Asteraceae species with a therapeutic activity referred to host and/or endophyte taxon.

Asteraceae Species and the Tissue of Endophytes Isolation	Main Therapeutic acTivities of the Host	Dominating Endophyte Genera	Main Activities of the Endophyte	Main Metabolites/Enzymes Linked to Endophyte Bioactivities
<i>Achillea millefolium</i> (stem, leaf, root)	Antioxidant, anti-inflammatory, antimicrobial, antitumor [63]	<i>Didymella</i> , <i>Septoria</i> , <i>Stemphylium</i> , <i>Cladosporium</i> , <i>Fusarium</i> , <i>Alternaria</i> , <i>Nemania</i>	Antitumor against lymphoblastic leukemia	L-asparaginase [56] *
<i>Achillea filipendulina</i> (stem, leaf)	Antioxidant, antidiabetic, anti-inflammatory, antimicrobial, antitumor, lubricant, antiparasitic [64,65]	<i>Plectosphaerella</i> , <i>Fusarium</i>	Antitumor against lymphoblastic leukemia	L-asparaginase [56]
<i>Anthemis segetali</i> (synonym of <i>Cota segetalis</i>) (stem, leaf, root, inflorescence)	Antioxidant anti-inflammatory, antitumor, antimicrobial, hepatoprotective [66]	<i>Alternaria</i> , <i>Aspergillus</i> , <i>Bjerkandera</i> , <i>Schizophyllum</i> , <i>Fusarium</i> , <i>Plenodomus</i> , <i>Cladosporium</i> , <i>Didymella</i> , <i>Stemphylium</i> , <i>Nemania</i> , <i>Phoma</i> , <i>Plectosphaerella</i> , <i>Sarocladium</i>	Antitumor against lymphoblastic leukemia	L-asparaginase [56]
<i>Anthemis triumfettii</i> (synonym of <i>Cota triumfettii</i> subsp. <i>Triumfettii</i>) (stem, leaf)	Antioxidant anti-inflammatory, antitumor, antimicrobial, hepatoprotective [66]	<i>Chaetosphaeronema</i> , <i>Stemphylium</i> , <i>Alternaria</i>	Antitumor against lymphoblastic leukemia	L-asparaginase [56]
<i>Artemisia annua</i> (stem)	Anti-inflammatory, antipyretic, antitumor, antifungal, antiparasitic, antiulcerogenic, cytotoxic [67–69]	<i>Colletotrichum</i>	Antibacterial against <i>Bacillus subtilis</i> , <i>Staphylococcus aureus</i> , <i>Sarcina lutea</i> , and <i>Pseudomonas</i> sp., and antifungal against <i>Candida albicans</i> and <i>Aspergillus niger</i>	3 β ,5 α -dihydroxy-6 β -acetoxy-ergosta-7,22-diene; 3 β ,5 α -dihydroxy-6 β -phenylacetyloxy-ergosta-7,22-diene; 3 β -hydroxy-ergosta-5-ene; 3-oxo-ergosta-4,6,8(14),22-tetraene; 3 β -hydroxy-5 α ,8 α -epidioxy-ergosta-6,22-diene [70]
<i>Artemisia vulgaris</i>	Antimalarial, anti-inflammatory, antihypertensive, antioxidant, antitumor, immunomodulatory, hepatoprotective, antispasmodic, antiseptic [71]	<i>Chalara</i>	Antibacterial against <i>B. subtilis</i> and antifungal against <i>C. albicans</i>	Isofusidienol A, B, C, and D [72]
<i>Artemisia mongolica</i> (stem)	Antimicrobial, insecticidal, antioxidant [73]	<i>Colletotrichum</i>	Antibacterial against <i>B. subtilis</i> , <i>S. aureus</i> , and <i>S. lutea</i> ; antifungal against <i>Bipolaris sorokiniana</i>	Colletotric acid [44]
<i>Atractylodes lancea</i>	Anti-inflammatory, hepatoprotective [74]	<i>Gilmaniella</i>	Antimicrobial	Jasmonic acid [75]
<i>Ayapana triplinervis</i>	Antimicrobial, anti-inflammatory [76]	<i>Paecilomyces</i> , <i>Aspergillus</i> , <i>Fusarium</i> , <i>Trichoderma</i> , <i>Penicillium</i> , <i>Curvularia</i>	Not investigated	Not investigated [77]

Table 1. Cont.

Asteraceae Species and the Tissue of Endophytes Isolation	Main Therapeutic Activities of the Host	Dominating Endophyte Genera	Main Activities of the Endophyte	Main Metabolites/Enzymes Linked to Endophyte Bioactivities
<i>Baccharis dracunculifolia</i>	Immunostimulatory, anti-inflammatory, cytotoxic, antitumor, hepatoprotective [78]	<i>Penicillium, Aspergillus, Fusarium, Colletotrichum</i>	Not investigated	Not investigated [79]
<i>Baccharis dracunculifolia</i> (leaf)	Antioxidant, anti-inflammatory, antiviral, antimicrobial, antiparasitic [80]	<i>Epicoccum, Pestalotiopsis, Cochliobolus, Nigrospora</i>	Antimicrobial	Not investigated [53]
<i>Bidens pilosa</i>	Antimalarial, anti-allergic, antihypertensive, antitumor, antidiabetic, anti-inflammatory, antimicrobial, antioxidant [81]	<i>Botryosphaeria</i>	Antifungal, cytotoxic, antiproliferative against carcinoma cell lines	Botryorhodine A and B [82]
<i>Cichorium intybus</i> (stem, leaf, root)	Antioxidant, anti-inflammatory, cardiovascular, hypolipidemic, antitumor, antidiabetic, antimicrobial, antiparasitic [83]	<i>Cladosporium, Epicoccum, Septoria, Plectosphaerella, Alternaria</i>	Antitumor against lymphoblastic leukemia	L-asparaginase [56]
<i>Gynura hispidia</i>	Anti-inflammatory, antiviral, hepatotoxic [84]	<i>Bipolaris</i>	Antifungal against <i>Cladosporium cladosporioides</i> , <i>C. cucumerinum</i> , <i>Saccharomyces cerevisiae</i> , <i>Aspergillus niger</i> , and <i>Rhizopus oryzae</i>	Bipolamide B [85]
<i>Helianthus annuus</i> (root)	Antibacterial, antioxidant, hepato-, nephro- and cardioprotective [86,87]	<i>Penicillium, Aspergillus</i>	Antifungal against <i>Sclerotium rolfsii</i>	Gibberellins (GA1, GA3, GA4, GA9, GA12, and GA20); organic acids (jasmonic, malic, quinic, salicylic, and succinic acid); siderophores [88,89]
<i>Laggera alata</i>	Anti-inflammatory, antioxidative, antibacterial, larvicidal [90]	<i>Podospora</i>	Larvicidal against <i>Anopheles gambiae</i>	Sterigmatocystin; 13-hydroxyversicolorin B [91]
<i>Matricaria chamomilla</i> (stem, leaf)	Anti-inflammatory, analgesic, antimicrobial, antispasmodic, sedative [92]	<i>Epicoccum, Didymella, Phoma</i>	Against lymphoblastic leukemia	L-asparaginase [56]
<i>Mikania glomerata</i> (leaf)	Anti-inflammatory, antispasmodic, anti-hemorrhagic, antiophidic, antiviral, antimicrobial [93]	<i>Diaporthe</i>	Antifungal against <i>Fusarium solani</i> and <i>Didymella bryoniae</i> ; antimicrobial against <i>Staphylococcus aureus</i>	Not investigated [94]
<i>Mikania laevigata</i> (leaf)	Anti-inflammatory, antispasmodic, antihemorrhagic, antiophidic, antiviral, antimicrobial [93]	<i>Hypoxyylon</i>	Not investigated	Not investigated [50]

Table 1. Cont.

Asteraceae Species and the Tissue of Endophytes Isolation	Main Therapeutic Activities of the Host	Dominating Endophyte Genera	Main Activities of the Endophyte	Main Metabolites/Enzymes Linked to Endophyte Bioactivities
<i>Notobasis syriaca</i>	Antioxidant, antimicrobial [95]	<i>Phomopsis</i>	Antimicrobial against <i>Legionella pneumophila</i> and <i>Escherichia coli</i>	Phomosine K; 2-hydroxymethyl-4 β ,5 α ,6 β -trihydroxycyclohex-2-en, (-)-phyllostine; (+)-epiepoxydon; (+)-epoxydon monoacetate [96]
<i>Smallanthus sonchifolius</i> (root, stem, leaf)	Antidiabetic, nutritious, fertility-enhancing, antioxidant, antimicrobial [97]	<i>Curvularia</i>	Antiparasitic against <i>Trypanosoma cruzi</i>	Stemphyperlylenol [98]
		<i>Papulaspora</i>	Cytotoxic against melanoma, colon, glioblastoma, and promyelocytic leukemia cell lines; antimicrobial	(24R)-stigmast-4-en-3-one; (22E,24R)-ergosta-4,6,8(14),22-tetraen-3-one; (22E,24R)-8,14-epoxyergosta-4,22-diene-3,6-dione [99]
		<i>Alternaria, Nigrospora, Phoma, Fusarium, Papulaspora</i>	Antifungal	Stemphyperlylenol, alterperlylenol, altertoxin I, alternariol, alternariol monomethyl ether [100]
		<i>Coniochaeta</i>	Antifungal against <i>Colletotrichum acutatum</i> , <i>C. fragariae</i> and <i>C. gloeosporioides</i>	Fatty acids: caproic, caprylic, cis-10-pentadecenoic, heptadecanoic, lauric, linoleic, myristic, oleic, palmitic, palmitoleic, pentadecanoic, stearic [101]
<i>Silybum marianum</i>	Antidiabetic, hepatoprotective, hypocholesterolemic, antihypertensive, anti-inflammatory, antitumor, antioxidant [102]	<i>Aspergillus</i>	Hepatoprotective	Silybin A, silybin B, isosilybin A [103]
<i>Tithonia diversifolia</i>	Anti-inflammatory, antimalarial, cytotoxic, gastroprotective, antimicrobial, antihyperglycemic [104]	<i>Colletotrichum</i>	Cytotoxic against the Jurkat tumor cell line	Nectriapyrone, tyrosol [105]
		<i>Phoma</i>	Cytotoxic	Anthraquinones [106]
<i>Trixis vauthieri</i> (leaf)	Antiparasitic [107]	<i>Alternaria</i>	Trypanocidal compound with inhibitory activity of trypanothione reductase	Altenusin [108]
<i>Urospermum picroides</i> (flower)	Anti-inflammatory, immunomodulatory, antioxidant, antimicrobial [109]	<i>Ampelomyces</i>	Cytotoxic against L5178Y cells; antibacterial against <i>Staphylococcus aureus</i> , <i>S. epidermidis</i> and <i>Enterococcus faecalis</i>	3-O-methylalaternin, altersolanol A [110]

Table 1. Cont.

Asteraceae Species and the Tissue of Endophytes Isolation	Main Therapeutic activities of the Host	Dominating Endophyte Genera	Main Activities of the Endophyte	Main Metabolites/Enzymes Linked to Endophyte Bioactivities
<i>Viguiera arenaria</i> (synonym of <i>Aldama arenaria</i>)	Antiparasitic, analgesic, anti-inflammatory, antitumor, antimicrobial [111]	<i>Phomopsis</i>	Antiparasitic against <i>T. cruzi</i>	3,4-dimethyl-2-(4'-hydroxy-3',5'-dimethoxyphenyl)-5-methoxy-tetrahydrofuran [112]
		<i>Colletotrichum</i>	Cytotoxic against leukemia tumor cells [106]	Nectriapyrone, tyrosol [105]
<i>Viguiera robusta</i> (synonym of <i>Aldama robusta</i>)	Anti-inflammatory, analgesic, antitumor, antiparasitic, antimicrobial [113]	<i>Chaetomium</i>	Cytotoxic against the Jurkat (leukemia) and B16F10 (melanoma) tumor cells; antibacterial against <i>S. aureus</i> and <i>E. coli</i>	Chaetoglobosin B [114]

* references in last column are linked to endophyte genera, activities, and metabolites.

4. Fungal Endophytes Associated with Asteraceae—Biochemistry

4.1. Plant Growth Promoting Secondary and Anti-Stress Metabolites

Asteraceae are leading examples of the synergistic effect of fungal endophytes in improving biotic and abiotic stress resistance and promoting plant growth because numerous species of this family possess extraordinary tolerance and competition skills. For example, Khan et al. [115] determined the growth-promoting ability of endophytic *Penicillium citrinum* in helping its plant host *Ixeris repens* in rapid colonization of the sand dunes. *P. citrinum* stimulated competition skills of the host plant through the production of secondary metabolites promoting plant growth, like gibberellins, and protective compounds, like mycotoxins, citrinin, and cellulose digesting enzymes [115]. *P. citrinum* and *Aspergillus terreus* were found to stimulate *H. annuus* growth and improve disease resistance due to the higher content of plant-defense hormones, salicylic, and jasmonic acids. The mentioned endophytes regulated oxidative stress of the host plant through activation of glutathione and polyphenol oxidases, alteration of catalase and peroxidase, as well as secretion of organic acids [88]. The individual or co-inoculation of endophytes increased amino acid content in sunflower (*H. annuus*) diseased leaves, delaying cell death, and consequently disturbing pathogen progression in plant tissues [88]. Ren et al. [75] showed that endophyte *Gilmaniella* sp. induced jasmonic acid production, which was recognized to be a signal compound promoting the accumulation of volatile oils in the Chinese medicinal plant *Atractylodes lancea*. The jasmonic acid acted as a downstream signal of nitric oxide and hydrogen peroxide-mediated production of volatile oil in the host. Various strains of *Penicillium* and *Aspergillus* species associated with Asteraceae were reported for gibberellins production [116]. *Penicillium* strains, especially MH7, produced nine gibberellins which significantly increased the growth and development of the host plant crown daisy (*Chrysanthemum coronarium*, synonym of *Glebionis coronaria*) [117]. The reactive oxygen species (ROS) production together with increased siderophore excretion by endophytes contributed towards improved growth and resistance against sunflower pathogens. Endophyte-origin ROS in plant roots are tackled by internal physiological plant apparatus resulting in an acute resistance against present and future stresses [89]. Huang et al. [58] compared the antioxidant capacity of plants used in Chinese traditional medicine, including mugworts: *Artemisia capillaris*, *A. indica*, and *A. lactiflora* (Asteraceae) and their endophytes. A fungal endophyte strain isolated from the flower of *A. capillaris* showed the strongest total antioxidant capacity. The antioxidant compounds detected in the highest amounts in both endophytic fungus and its host *A. indica* were chlorogenic and di-O-caffeoylquinic acids, and the volatile compound artemisinin. Both chlorogenic acid and artemisinin acted as antioxidant, antimutagenic, immunomodulatory, and antiviral. The production of the same bioactive natural compounds, as well as some of those found in *A. indica* and its fungal endophytes, was suggested. In general, phenolic compounds, including phenolic acids, flavonoids, tannin constituents, hydroxyanthraquinones, and phenolic terpenoids as well as volatile or aliphatic constituents were major substances in the fungal endophyte cultures and host plant extracts responsible for high antioxidant activity of all investigated Chinese medicinal plants [58]. In terms of abiotic and biotic stress, fungal endophytes conferred resistance against drought, salinity, heat stress, and enhanced resistance against pathogens and insects. The different mechanisms can stay behind the competitive success of invasive Asteraceae species like crofton weed (*A. adenophora*). The most abundant endophytic fungus isolated from this species was *Colletotrichum* sp. which has pathogenic effects on other plants. Spreading *Colletotrichum* spores could be a competitive advantage for *A. adenophora* as it was hypothesized by Fang et al. [62]. The recognition of endophyte roles in host plant expansion and competition mechanisms enables the application or modification of cultivation techniques dedicated to particular medicinal Asteraceae species, especially those with promising therapeutic and economical potential.

4.2. Antibacterial Secondary Metabolites

The best criterion for host plant selection in order to investigate the endophytes with potential antimicrobial activity is the plant traditionally used for the treatment of infections [118]. Plant-associated

fungi may interact using, inter alia, antibiotic molecules, so the production of antibiotics and the parallel development of antibiotic-resistance mechanisms can spread in dynamic microbiota/plant systems by bacterial mobilization and horizontal gene transfer [119,120]. In recent years, the number of multidrug-resistant microorganisms have been a growing concern for public health worldwide. The key determinants of bacteria drug resistance are inactivation of the antibiotics, changes in bacterial targets, and restricted entry of antibiotics by less permeable drug transporters [121]. Asteraceae/fungal endophytes consortia could be a source of active compounds targeted against many drug-resistant microorganisms [122,123]. A fungus *Colletotrichum* sp. was isolated from the stems of *Artemisia annua* and characterized as a source of ergosterol derivatives (Figure 3), with inhibitory potential against both Gram-negative and -positive bacteria, such as *Pseudomonas* sp. and *Bacillus subtilis* with minimal inhibitory concentrations (MICs) ranging from 25 to 75 $\mu\text{g mL}^{-1}$ [70]. *Colletotrichum* sp. can also produce plant hormones such as indole-3-acetic acid (IAA), up-regulating host growth. Both mechanisms of action, namely antibiosis and growth promotion, can enhance adaptability and pathogen resistance of a host plant. At the same time, Zou et al. [44] isolated from the stem of *Artemisia mongolica* an endophytic fungus *Colletotrichum gloeosporioides*, synthesizing colletotric acid with antibacterial activity against *B. subtilis*, *Staphylococcus aureus*, *Sarcina lutea*, and *Pseudomonas* sp. with MICs of 25, 50, and 50 $\mu\text{g mL}^{-1}$, respectively, and inhibited a pathogenic fungus *Helminthosporium sativum* (current name *Bipolaris sorokiniana*) with a MIC of 50 $\mu\text{g mL}^{-1}$. This was the first report of *C. gloeosporioides* as a fungal endophyte in the Asteraceae, although it was previously mentioned as an endophyte of plants belonging to the other families. The isocoumarins and naphthalene derivatives produced by *Papulaspora immersa*, a fungal endophyte isolated from the Andean tuber crop, the yacon (*S. sonchifolius*), presented antimicrobial activities and could act synergistically [99]. Interestingly, some fungal metabolites were identified as constituents of an extract derived from a healthy Asteraceae, prickly goldenfleece (*Urospermum picroides*), indicating that the production of bactericides by the fungal endophyte *Ampelomyces* sp., proceeds also in situ within the host plant [110]. Among seven phomisine derivatives isolated from *Phomopsis* sp., an endophyte of the Syrian thistle (*Notobasis syriaca*), phomisine K had strong antibacterial activity against *Legionella pneumophila* Corby, *Escherichia coli* K12 with MIC 25 and 100 $\mu\text{g mL}^{-1}$, respectively [96]. Endophyte colonization offers protection from various stressors, such as toxins which affect plant pathogens by disrupting the cellular membrane and inducing cell death. Such ecological relationships were recorded for the mentioned Asteraceae/endophyte systems.

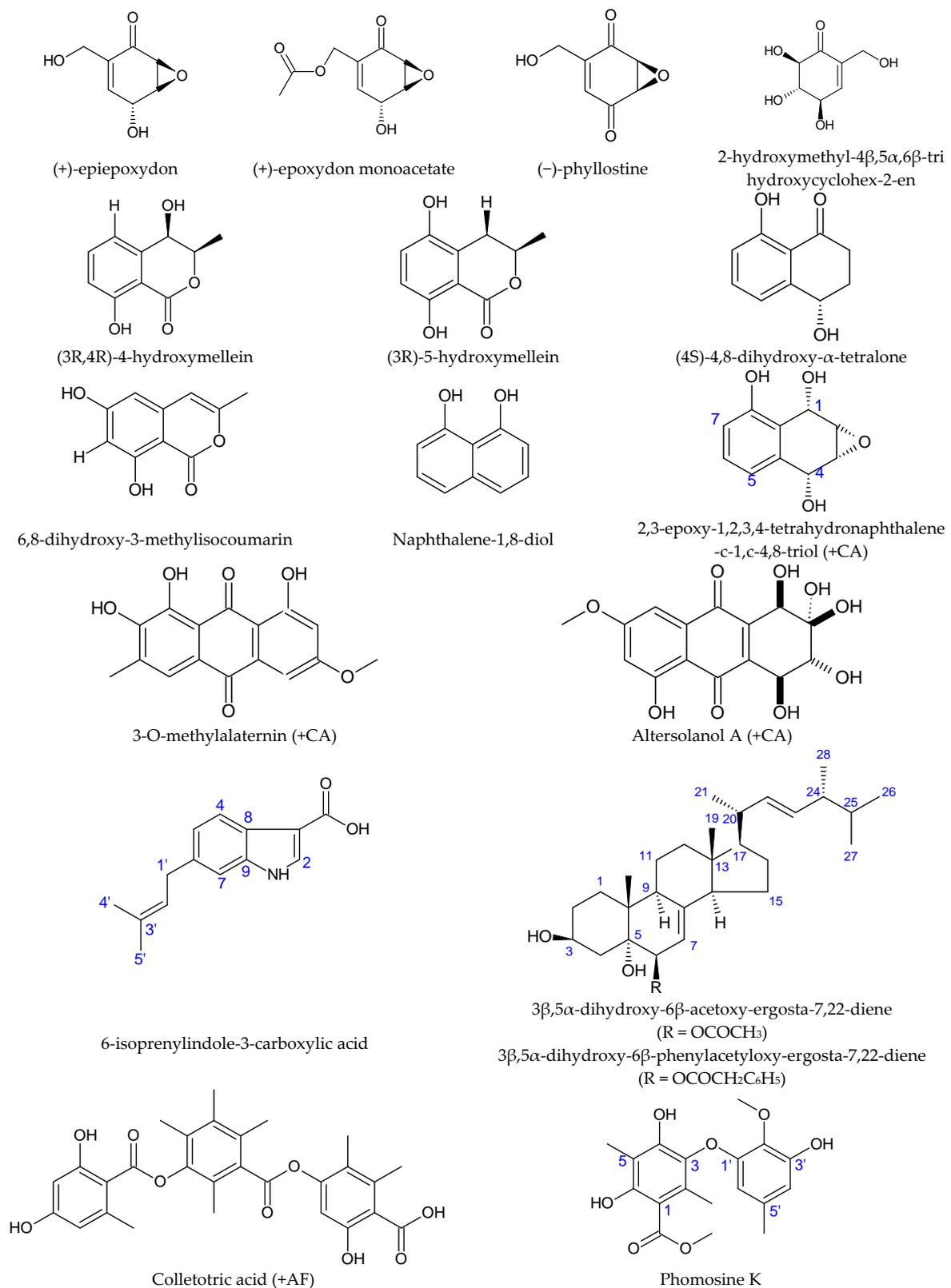


Figure 3. The molecular structure of chosen specific compounds with antibacterial activity synthesized by fungal endophytes associated with Asteraceae species [44,70,96,99,110]; +AF—antifungal activity; +CA—cytotoxic activity.

4.3. Antifungal Secondary Metabolites

Colonization of the host plant by endophytes and pathogens depends on their adaptations to the host environment but also the innate host defense mechanism and variation in virulence. A few reports on endophytic fungi, protecting against other fungal infection, found in association with Asteraceae species, especially *Viguiera* spp. (syn. *Aldama* spp.) were published, and several new compounds were described but their biological action needs future research [17,22,68,75,78,101]. *Ampelomyces* spp. were widely studied as the first fungi used as biocontrol agents of powdery mildews [122]. Chagas et al. [100] investigated the interactions between the fungal endophytes that cohabit *S. sonchifolius*. They found that *Alternaria tenuissima* synthesized some polyketides, including antifungal stemphyterylol in the presence of endophytic *Nigrospora sphaerica* (Figure 4). *A. tenuissima* is characterized by a slower growth rate than *N. sphaerica*, so specific antifungal compounds might control the growth rate of *N. sphaerica* during host plant colonization, without any damage to the host plant tissues. The competition of fungal endophytes colonizing the same host plant stimulates the production of metabolites that could decrease the growth of particular fungi species without damaging the host plant and maintaining the symbiosis [100]. A closer metabolome relationship was found for *S. sonchifolius* and endophytic fungus *Coniochaeta ligniaria*. Both symbionts produced the same antifungal fatty acids: caproic, caprylic, and palmitic acids at high concentrations which might raise the resistance of *S. sonchifolius* to fungal pathogenic attacks and *C. ligniaria* to fungi competing within the host tissues [101]. *B. trimera* is a native medicinal plant of the Brazilian savannah. Vieira et al. [53] isolated from the leaves of this species 23 fungal taxa, inter alia, *Epicoccum* sp., *Pestalotiopsis* sp., *Cochliobolus lunatus*, and *Nigrospora* sp., which showed antifungal activity against *Paracoccidioides brasiliensis*. Additionally, the fungi isolated from different host plants displayed distinct antimicrobial activities, so the endophytic richness and the antimicrobial activity were closely correlated. The endophyte fungus *Preussia* sp. revealed strong antifungal activity, related to the synthesis of anthraquinones, auranticins, culpin, cycloartane triterpenes diphenyl ether, spirobisnaphthalenes, and thiopyranchromenones [53,124]. However, metabolome analysis of *Preussia* sp. isolated from Asteraceae herb carqueja (*B. trimera*) confirmed antioxidant but not antifungal activity of isolated compounds, namely preussidone, 1',5-dimethoxy-3,5'-dimethyl-2,3'-oxybiphenyl-1,2'-diol, 5-methoxy-3,5'-dimethyl-2,3'-oxybiphenyl-1,1',2'-triol, and cyperin [124]. Waqas et al. [88,89] determined the inhibitory effect of two fungal endophytes, *P. citrinum* and *A. terreus*, against *Sclerotium rolfsii*, a soilborne plant pathogen which causes root rot, stem rot, collar rot, wilt, and foot rot diseases in *H. annuus*. The antifungal activity of *Penicillium* and *Aspergillus* strains was linked with synthesis of gibberelins, organic acids, and siderophores. Two new fatty acid amides, bipolaramides A and B, were isolated from endophytic fungus *Bipolaris* sp., but only bipolaramide B revealed bioactivity against *Cladosporium cladosporioides*, *C. cucumerinum*, *Saccharomyces cerevisiae*, *Aspergillus niger*, and *Rhizopus oryzae* [85]. Fungal endophytes possess multiple balanced antagonisms, namely with the other microbial inhabitants of the host plant and with the host plant itself, to support the growth conditions enabling reproduction. Most genes involved in secondary metabolite synthesis in fungi are activated while being co-cultured in plant and/or with other microbes, but they are generally silent in cultures, confirming that multiple antagonisms are involved in endophytism [22]. Three strains of endophytic fungus *Diaporthe citri* isolated from Brazilian medicinal vine, guaco (*Mikania glomerata*) presented 60% inhibition index of mycelia growth against *Fusarium solani* and 66% against *Didymella bryoniae* [94]. The mechanisms of inhibition were not tested in the cited reference, but the authors stated that endophytic microorganisms with the highest inhibition indices were considered candidates for tests involving the production of secondary metabolites with potential antimicrobial activity.

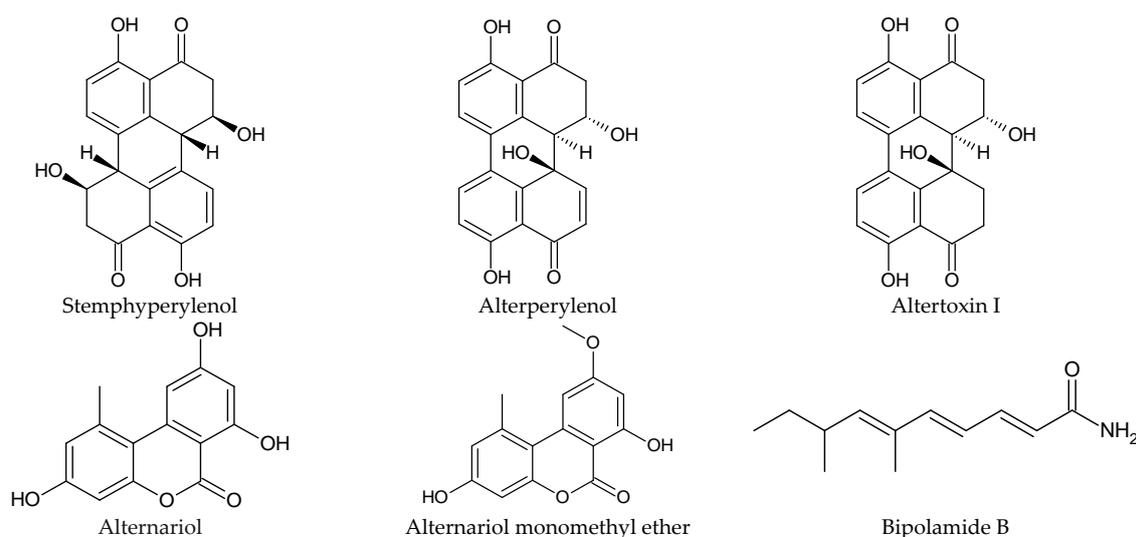


Figure 4. The molecular structure of chosen specific compounds with antifungal activity synthesized by fungal endophytes associated with Asteraceae species [85,100].

4.4. Antiparasitic Secondary Metabolites

Cota et al. [108] isolated altenusin from an *Alternaria* sp. endophytic in *Trixis vauthieri* collected in Brazil (Figure 5). This medicinal plant was reported as containing trypanocidal compounds of trypanothione reductase inhibitory activity. Meanwhile, the organic extract of the culture of *Alternaria* sp. inhibited trypanothione reductase by 99%, when tested at 20 mg mL^{-1} . The mentioned report was the first one concerning fungal metabolites with trypanothione reductase inhibitory activity, which can be used for the development of new chemotherapeutic agents to treat trypanosomiasis and leishmaniasis. *Trypanosoma cruzi* is a parasitic euglenoid causing Chagas disease in humans, and *Leishmania tarentolae* is a protozoan parasite of geckos, which might also be capable of infecting mammals [125]. Verza et al. [112] determined that endophytic fungus *Phomopsis* sp., obtained from *Viguiera arenaria* (synonym of *Aldama arenaria*), led to the formation of a new compound able to transform the tetrahydrofuran lignan, (–)-grandisin to 3,4-dimethyl-2-(4′-hydroxy-3′,5′-dimethoxy phenyl)-5-methoxy-tetrahydrofuran, which also showed trypanocidal activity against *T. cruzi*. Guimarães et al. [105] isolated 30 endophytic fungi from the leaves and four from the roots of *V. arenaria* and five endophytes were isolated from the leaves of *Tithonia diversifolia*, collected in Brazil. The ethyl acetate extract of the *Diaporthe phaseolorum* isolate’s fermentation broth showed strong inhibition of glyceraldehyde 3-phosphate dehydrogenase of *T. cruzi* and adenine phosphoribosyltransferase of *L. tarentolae*. The mosquito *Culex quinquefasciatus* acts as a vector of *Wuchereria bancrofti* which causes the disease lymphatic filariasis, commonly known as elephantiasis. Belonging to the Asteraceae family, *Ageratum conyzoides*, native to Pakistan, has antilarvicidal effects against the mosquito larvae of *C. quinquefasciatus*, *Aedes aegypti*, and *Anopheles stephensi*. Endophytic actinomycetes, *Streptomyces* spp., isolated from mentioned Asteraceae species showed strong larvicidal activity at the fourth instar stage [126]. Xanthenes, sterigmatocystin, and anthraquinone derivative, 13-hydroxyversicolorin B from the culture broth of the endophytic fungus *Podospora* sp., isolated from the Kenyan medicinal plant *Laggera alata*, might be used as natural mosquito larvicides [91]. The easily biodegradable endophyte metabolites could be a base for the development of modern techniques providing efficient insect control, without negative effects on the non-target population and environment.

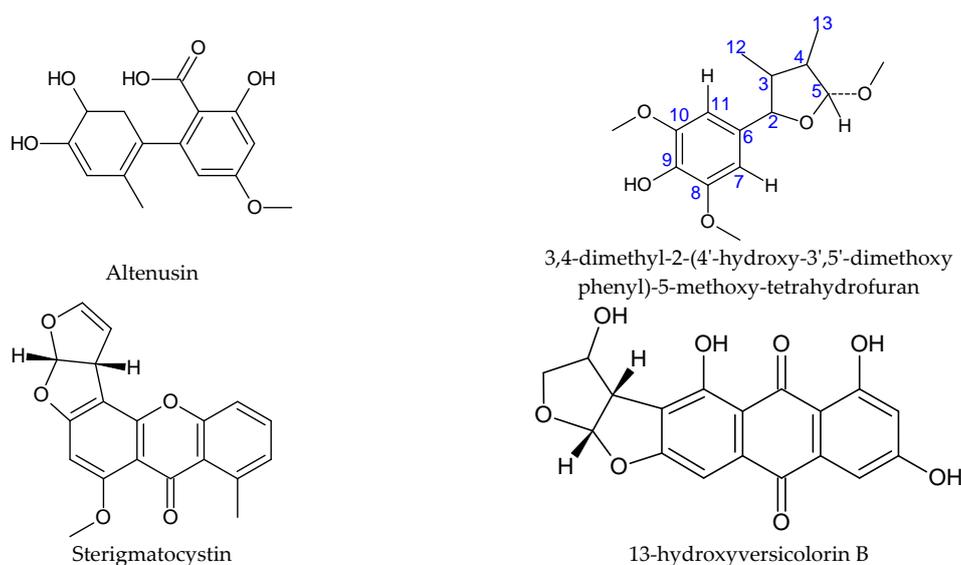


Figure 5. The molecular structure of chosen specific compounds with antiparasitic activity synthesized by fungal endophytes associated with Asteraceae species [91,108,112].

4.5. Cytotoxic Secondary Metabolites

The major difficulty in the treatment of cancer is the increase in drug resistance of commonly used chemotherapeutic agents, so the crucial task is to find out the novel compounds with high efficacy and low toxicity. The research and registration of new antitumor drugs are mostly based on the compounds extracted from medicinal plants including those of endophyte origin [127]. Martínez–Klimova et al. [5] found the endophytes that produce antibiotic metabolites belonging to phylum Ascomycota, which were isolated from the Asteraceae, Fabaceae, Lamiaceae, and Araceae families. The therapeutic activity of fungal endophytes was related to the production of compounds inhibiting the drug transporters of tumor cells. Moreover, the use of secondary metabolites produced by endophytes could mediate drug resistance reversal in cancer cells. A few reports are pointing out the use of endophytes isolated from Asteraceae species as a source of antitumor compounds targeted in the most common lines of cancer cells (Figure 6). Nectriapyrone, produced by the endophytic fungus *Glomerella cingulata*, a teleomorph stage of *C. gloeosporioides*, isolated from *V. arenaria* and *T. diversifolia* showed relevant cytotoxic activity towards tumor cells [105]. In the case of *Chaetomium globosum*, a fungal endophyte associated with *Viguiera robusta*, chaetoglobosins showed inhibition of Jurkat (leukemia) and B16F10 (melanoma) tumor cells with 89.55% and 57.1% inhibition at 0.1 mg mL^{-1} , respectively [114]. Gallo et al. [99] isolated a fungus *P. immersa* from roots and leaves of *S. sonchifolius*. *P. immersa* extracts displayed strong cytotoxicity due to newly described secondary metabolites, i.e., 2,3-epoxy-1,2,3,4-tetrahydronaphthalene-c-1,c-4,8-triol, which showed highest activity against the human tumor cell lines MDA-MB435 (melanoma), HCT-8 (colon), SF295 (glioblastoma), and HL-60 (promyelocytic leukemia), with the half maximal inhibitory concentration (IC₅₀) values of 3.3, 14.7, 5, and 1.6 μM , respectively. Moreover, sitostenone and tyrosol, other *P. immersa* secondary metabolites, showed anticancer effects when applied with isocoumarin [99]. The fungal endophytes of Asteraceae, especially the members of genera *Fusarium*, *Plectosphaerella*, *Stemphylium*, *Septoria*, *Alternaria*, *Didymella*, *Phoma*, *Chaetosphaeronema*, *Sarocladium*, *Nemania*, *Epicoccum*, and *Cladosporium* can produce the anticancer enzyme L-asparaginase used in the treatment of acute lymphoblastic leukemia. The isolates of fungi *Fusarium proliferatum* and *Plectosphaerella tracheiphilus*, obtained from an Asteraceae host *C. segetalis*, exhibited a maximum enzyme activity with 0.492 and 0.481 unit mL^{-1} , respectively [56]. The milk thistle (*Silybum marianum*) is known as a source of silymarin, a mixture of flavonolignans used in cancer chemoprevention and hepatoprotection. El-Elimat et al. [103] showed that a fungal endophyte, *Aspergillus iizukae* (current name *Fennellia flavipes*), isolated from leaves of *S. marianum* can synthesize similar compounds as a host plant, namely silybin A, silybin

B, and isosilybin, the constituent compounds of silymarin. Endophytic fungi that can produce the same compounds of their associated host plants could be a sustainable and alternative source for secondary metabolites.

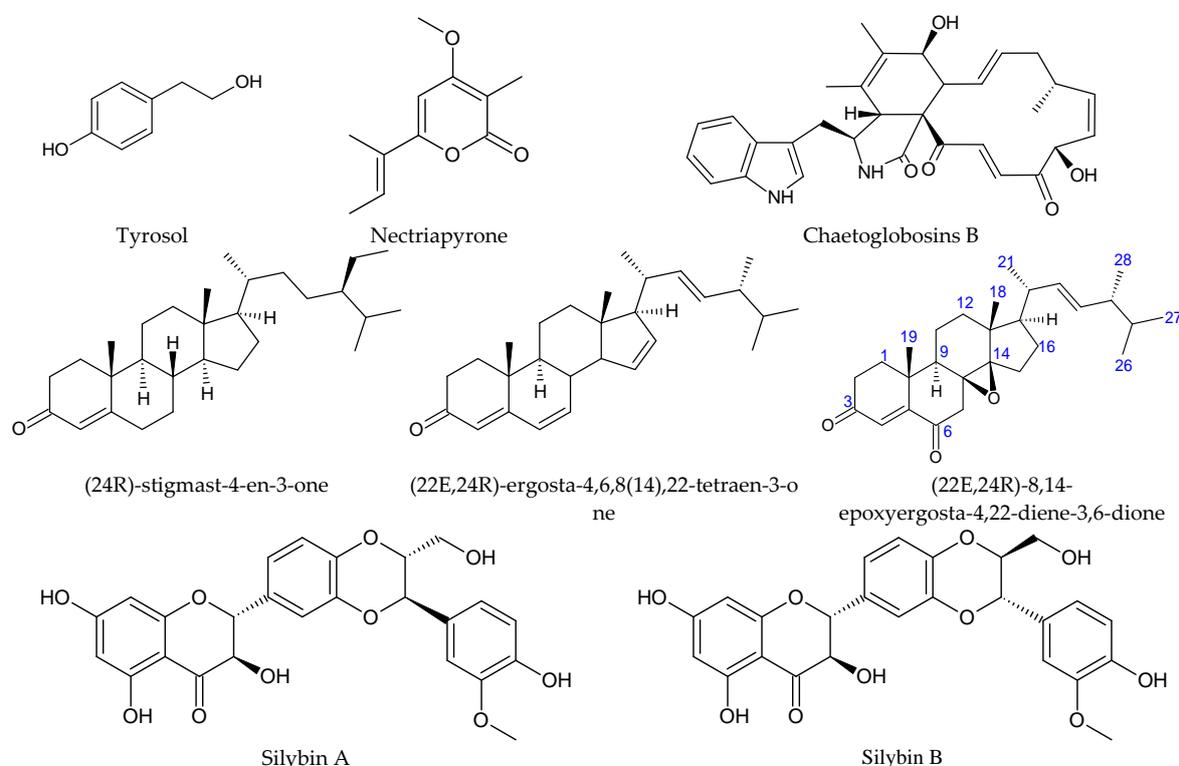


Figure 6. The molecular structure of chosen specific compounds with cytotoxic activity synthesized by fungal endophytes associated with Asteraceae species [99,103,105,110,114].

5. Review Methodology

The leading scientific databases dedicated to multidisciplinary as well as agricultural, biological, biomedical, and pharmacological sciences were screened. Relevant literature dated to the period 2000–2020 was collected, analyzed, and selected considering (i) the reports on endophyte isolation from the species of Asteraceae family, (ii) the reports on therapeutic utilization of the host plant or/and an endophyte, (iii) the reports on in vitro and in vivo bioactivity of chemical compounds produced by a host plant or/and an endophyte. Plant names were verified according to the Global Biodiversity Information Facility [128] and The Plant List [34], endophyte taxa were verified according to MycoBank database [129]. For clarity, the validated endophyte names used in the referenced literature were implemented in the text. In the tables and figures, the current taxa classification and nomenclature were used. Chemical structures were elaborated on the basis of referred publications, for new isolated compounds the number of C atoms was presented.

6. Conclusions

A growing spectrum of literature indicates that endophyte fungi colonizing different species of Asteraceae are responsible to some degree for their therapeutic potential reported in ethnobotanical and modern literature. Endophyte fungi are elements of a complex web of interactions of the plant host/endophyte/phytopathogen, and hence all elements of this system are expected to produce bioactive compounds that can improve their ability to survive in such a dynamic environment. Endophytes were involved in the superior adaptability and competitiveness reported for Asteraceae hosts and their evolutionary success. Plant/endophyte interactions regulated the energy costly process of production

of secondary metabolites possessing therapeutic properties. In the case of the Asteraceae species analyzed, the host tissue's environment was more crucial than plant taxonomy for shaping the diversity and metabolite profile of fungal endophytes. Most endophyte fungi isolated from Asteraceae plants were wide-spreading. Despite that, they produced very specific secondary metabolites in planta and in vitro. The interactions between the endophyte and its host controlled by specific chemical compounds are dynamic and difficult to analyze but crucial for the composition of the medicinal plant extracts and their standardization.

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