

Endophytes of Terrestrial Plants: A Potential Source of Bioactive Secondary Metabolites

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Abstract Endophytes are plant inhabiting microorganisms that possess a big and untapped source of natural products with unique chemical structures and biological activities for pharmaceutical and agriculture industry. About, several hundred of endophytes are associated with plants. Metabolites isolated from endophytes with diverse structures belong to alkaloids, steroids, terpenoids, flavonoids, phenols, flavonoids and others. The discovery of an array of therapeutic products has diverted the scientist's interest from plants to these microorganisms. Hundreds of natural compounds have been obtained and structurally classified while other new active metabolites are under investigation. This present review is an approach to summarize some chemical classes of bioactive compounds obtained from these microorganisms and paving the way for future work.

Keywords: bioactivities, endophytes, natural products, secondary metabolites

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1. Introduction

Endophytes are microorganisms (fungi, bacteria and actinomycetes) inhabiting healthy plant intercellularly and/or intracellularly without causing any visible symptoms of disease [1,2]. De Bary was first to introduce the term "Endophyte" in 1866 [3], which was initially referred to all those organisms that found within a plant causing nonvisible infections entirely within plant tissues showing no apparent symptoms of disease [1]. Endophytes dwell all plant species reported to date throughout the globe in a symbiotic relation [4].

During the last decades, endophytes have been searched out for important metabolites. It is evident from research that endophytes are new source and gold-mine of novel natural products to treat different ailments in human and plants. They are synthesizers of chemical entities that are extensively used as agrochemicals, antibiotics, immunosuppressant, antiparasitics, and anticancer agents [5]. As a routine work, medical herbs are directly used for therapeutic components to isolate and characterize. However, the discovery of plant endophytes with potential of medicinal compounds tremendously attracted the interest of chemists to search for new drugs. Among these microbes, endophytic fungi have been found bountiful of unexploited biologically active small molecules [6].

Based on the studies about microorganisms, actinomycetes and fungi have been reported to be the most productive

source of therapeutic agents. Fungi are vital for a balanced ecosystem and biodiversity conservation [7,8]. The endophyte was first discovered in 1904 [9]. Endophytes attracted dramatic attention when their ability of synthesizing biologically active components having structures were realized. Hence, for the last 20 years, over 100 endophytes of various hosts have been investigated for chemical and biological assessment of a huge number of metabolites. Among them, many have been found to have unique structures and interesting biological functions. Gusman and Vanhaelen first isolated natural compounds from 38 endophytic fungi and studied their pharmacology [10].

About 138 natural products of endophytes were communicated by Tan and Zou [11]. These secondary metabolites may be mainly classified as; alkaloids, flavonoids, phenolic acids, quinones and many others [12]. Schulz et al. [13]. Strobel [14,15] and Strobel et al. [16] have explained their own research on endophytes. This review aims to present some previous and new interventions related to isolation of metabolites from endophytes.

1.1. Types of Endophytes

Endophytes have been described as; Bacterial endophytes are found best producers of different therapeutic compounds. About 76% of them obtained from *Streptomyces* [17]. They are either gram-positive or gram-negative, such as, *Acinetobacter*, *Agrobacterium*, *Bacillus*, *Microbacterium* and *Pseudomonas* etc. [18]. More than 200 genera serve as endophytes [19].

Actinomycetes possessing mycelium like fungus and forms spores. These microorganisms were thought out transitional forms between the fungi and bacteria [20,21]. They are bacteria like but actinomycetes have thin cells and an organized chromosome in a prokaryotic nucleoid and a peptidoglycan cell wall. This class has demonstrated synthesis of numerous chemical entities of unique structures that have significant medicinal value [22,23].

Fungi are heterotrophic organisms with various life cycles that inhabit symbiotically a wide variety of autotrophic organisms [24]. Endophytic fungi have been branched into clavicipitaceous and non-clavicipitaceous endophytes. The first are inhabitants of some grasses while the other of non-vascular plants and higher plants restricted to Ascomycota or Basidiomycota group. Most of known antibiotic and anticancer drugs were derived from these organisms. For example, Penicillins and Taxol were potent drugs isolated from *Penicillium* sp. and *Taxomyces andreanae*, respectively. More than 20,000 bioactive products having unprecedented structures have been reported in the literature [25].

1.2. Distribution in Nature

Endophytes are ubiquitous and almost all vascular plant species studied to date were found to anchorage endophytic bacteria and/or fungi [26,27]. Endophytes play a vital role in biodiversity of microbes [28]. They are host specific and a plant may harbor many species. The population of endophytes also depends on environmental conditions of the host plants [29], and the tropical areas may have variegated endophyte profile. Tropical endophytes may be hyper diverse and unevenly scattered in a specific area [27]. Genotypic diversity is also found in some endophytes of conifers and grasses. Hence, endophytes are omnipresent depending on host and location for their population [30,31,32,33].

2. Isolation and Identification

Different methods of isolation like Agar Plate Method and Standard Moist Blotter method are used to isolate mycoflora from medicinal plants [34,35,36]. Cultivation-independent assays and *in situ* hybridization-confocal laser scanning microscopy are used for their detection [37,38]. Mostly isolation from sterilized tissue of inhabitant's plant is used to detect endophytes. Different methods of isolation have also been described by Rehman et al. [39] and Karunai & Balagengatharathilagam [40].

Morphological characteristics and biochemical tests are also usually used to identify bacteria, fungi, and actinomycetes [41,42]. Due to recent advancement in molecular studies, ribosomal DNA Internal Transcribed Spacer (ITS) sequence technique is a frequent practice to identify microorganisms [43]. Primarily, *Pleurostoma* and *Chaetomium* along with others were identified as endophytes by ITS technique [44].

3. Review: Bioactive Compounds

During the last few years a number of secondary metabolites originated from endophytes have been

documented. They are indispensable due to their chemical and diverse biological properties. Some of the bioactive compounds are reviewed under the following groups.

3.1. Alkaloids

Alkaloids are naturally occurring nitrogenous chemical compounds of plant origin. They have pronounced physiological effects on humans and other animals.

Camptothecin (**1**, CPT) is topoisomerase inhibitor and most potent cytotoxic compound [45,46] having anticancer activities. CPT and its derivatives such as 10-hydroxycamptothecin (**2**) and 9-methoxycamptothecin (**3**) were derived from *Fusarium solani*; inhabitant of *Apodytes dimidiata* [47]. *Eupenicillium* sp. was isolated from *Murraya paniculata* and produced alanditrypinone (**4**), alantryphenone (**5**), alantrypinene B (**6**) and alantryleunone (**7**) [48]. Asperfumoid (**8**) is a new alkaloid and was isolated from *Aspergillus fumigatus* CY018, an endophyte of *Cynodon dactylon*. This metabolite caused inhibition of *Candida albicans* [49]. Aspernigerin (**9**) was produced by *Aspergillus niger* IFB-E003 (having same host), demonstrated growth inhibition of tumor cells [50].

Phomoenamide (**10**) was isolated from fungus *Phomopsis* sp. PUS-D15; an endophyte of *Garcinia dulcis* Kuiz leaves. The compound has antibacterial activity against *Mycobacterium tuberculosis* H37Ra [51]. An endophyte *Xylaria* sp. was cultured from *Ginkgo biloba* L., which produced a compound 7-amino-4-methylcoumarin (**11**) having strong antibacterial and antifungal activities [52]. A novel product; 7-*O*-methylvariecolortide A (**12**) was produced by an endophyte found inside the stems of *Hibiscus tiliaceus* [53]. Phomopsichalasin (**13**), a novel alkaloid produced by fungus *Phomopsis* living on *Salix gracilostyla*. The compound proved to have antibacterial and antifungal properties [54].

Chaetoglobosins A (**14**) and C (**15**), were obtained from *C. globosum*; an endophyte of *Ginkgo biloba*. These two compounds proved to have antibacterial activity against *Mucor miehei*. [55]. Fungus *Cladosporium* (CLJ-2) derived from young *C. ledgeriana* stems resulted a metabolite, named cinchonine (**16**). The compound has cytotoxic potency for 95-D and HepG2 cell lines [56]. Herquiline B (**17**) having antimicrobial activities was derived from endophytic fungus *Talaromyces pinophilus* of *Arbutus unedo* [57]. Vincristine (**18**) and vinblastine (**19**) were detected in the extracts of endophyte *Penicillium* sp.-VE89L and three strains identified as *Alternaria* sp.-VM84L, *Cladosporium* sp.-VE92L and *A. amstelodami*-VRI77L, respectively. These endophytes were isolated from leaves of *V. erecta*. Both compounds have shown pronounced growth inhibition with cultured cells of HBL-100 [58].

3.2. Steroids

A steroid is a biologically active organic compound with four rings of carbon atoms arranged in a specific molecular configuration. Examples include lipid cholesterol and anti-inflammatory drug dexamethasone etc. [59]. Isolation of novel compounds, (14 β ,22 E)-9, 14-dihydroxyergosta-4,7,22-triene-3,6-dione (**20**) and (5 α ,6 β ,15 β ,22 E)-6-ethoxy-5,15-dihydroxyergosta-7,22-

dien-3-one (**21**) was achieved from *Phomopsis* sp. of *Aconitum carmichaeli* [60]. Both compounds showed moderate antifungal properties. A novel (22*E*, 24*R*)-3-acetoxy-19(10→6)-abeo-ergosta-5,7,9,22-tetraen-3β-ol (**22**) was resulted by *Colletotrichum* sp. obtained from *Ilex canariensis* [61]. Two new steroids namely 3β, 5α-dihydroxy-6β-acetoxyergosta-7, 22-diene (**23**) and 3β, 5α-dihydroxy-6β-phenyl-acetyloxyergosta-7, 22-diene (**24**) were characterized from the liquid culture of fungal endophyte *Colletotrichum* sp. of *A. annua*, having antifungal activities [62].

A novel polyhydroxylated C₂₉-sterol, named globosterol (**25**), together with one known tetrahydroxylated ergosterol (22*E*,24*R*)-ergosta-7,22-diene-3β,5α,6β,9α-tetraol (**26**) has been isolated from the cultures of an endophytic fungus, *Chaetomium globosum* ZY-22 originated from the plant *Ginkgo biloba* [63]. A steroid named 5α, 8α-epidioxyergosterol (**27**) was derived from *Nodulisporium* sp. residing on *Juniperus cedre* [64]. Solanionic acid (**28**) was produced by *Rhizoctonia solani* inhabiting tubers of *Cyperus rotundus*. It caused strong inhibition of Gram-positive bacterial strains [65]. Novel metabolites, named fusaristerols B (**29**), C (**30**) and D (**31**) were discovered from *Fusarium* sp. inhabiting *Mentha longifolia* L. (Labiatae) roots. The compounds possessed 5-LOX inhibitory activity to treat different inflammatory disorders [66].

3.3. Terpenoids

Terpenoids are a large and diverse class of naturally occurring organic chemicals derived from five-carbon isoprene units. Terpenoids comprise the largest group of natural products. A number of terpenoids have been isolated from plant endophytes. The xylarenones A (**32**), B (**33**) and xylarenic acid (**34**) were obtained from the endophytic fungus *Xylaria* sp. NCY2, obtained from *Torreya jackii*. The compounds exhibited moderate antitumor activities against HeLa cells [67]. Endophyte *Phomopsis cassiae* associated with *Cassia spectabilis* resulted two diastereoisomeric compounds named (7*S*, 9*S*, 10*S* and 7*S*, 9*R*, 10*S*)-3,9,12-trihydroxycalamenenes (**35**, **36**), 3,12 dihydroxycalamenene (**37**), 3,12-dihydroxycadalene (**38**) and 3,11,12-trihydroxycadalene (**39**) [68]. Botryosphaerins A-E (**40-44**) along with acrostalidic acid (**45**), acrostalic acid (**46**), agathic acid (**47**) and isocupressic acid (**48**) were identified from *Botryosphaeria* sp. MHF derived from *Maytenus hookeri* [69]. Endophyte *Xylaria* sp. PSU-D14 resulted xylaroside A (**49**) and B (**50**). While *Eutypella scoparia* PSU-D44 produced scoparanes A (**51**), B (**52**) and diaporthins A (**53**), B (**54**). Both species are associated with *Garcinia dulcis* [70,71].

Endophytic fungus *Phomopsis* sp. XZ-26 collected from *Camptotheca acuminata* produced a new monoterpene termed as dihydroxysabinane (**55**) [72]. The preaustinoid B2 (**56**), preaustinoid A3 (**57**), austinolide (**58**) and iso-austinone (**59**) were identified from fungi *Penicillium* sp. found in the root bark of *Melia azedarach* [73]. Fungi *P. brasilianum* (inhabiting same host) resulted novel compounds, called preaustinoid A1 (**60**), A2 (**61**) and B1 (**62**) [74]. Guanacastepene A (**63**) and guanacastepene (**64**) were characterized from endophytes of *Daphnopsis americana*. Whereas, periconicin A (**65**) and perieonin (**66**) were discovered from *Periconia* sp. These four novel diterpenoids proved as antibiotics [75]. Three new metabolites, namely lithocarin B (**67**), C (**68**) and D (**69**) were obtained from the endophytic fungus *Diaporthe lithocarpus* A740 derived from *Morinda officinalis*. Compounds B and C showed weak inhibitory activities against four tumor cell lines [76].

3.4. Quinones

Quinones are a class of cyclic organic compounds containing two carbonyl groups, >C=O, either adjacent or separated by a vinylene group, -CH=CH-, in a six-membered unsaturated ring.

Herbarin (**70**) and its analogue herbaridine A (**71**) have been isolated from an endophytic fungus *D. nanum* derived from *F. religiosa* [77]. Three new compounds named preussomerin J (**72**), K (**73**) and L (**74**) having antibacterial and antifungal activities were synthesized by an endophytic fungus *Mycelia sterile* isolated from the roots of *Atropa belladonna*. [78]. *Ampelomyces* sp., an endophyte of *Urospermum picroides*, produced 3-*O*-methylalaternin (**75**) and tetrahydroanthraquinone altersolanol A (**76**). Both compounds were active against the bacteria *S. aureus*, *S. epidermis* and *E. faecalis* at different MIC levels [79].

A bioactive compound, termed as 4-dehydroxyaltersolanol A (**77**) was produced by an endophytic fungus, *Nigrospora oryzae*, isolated from leaves of *Combretum dolichopetalum*. The compound proved to be cytotoxic against mouse lymphoma cells [80]. *Bipolaris sorokiniana* A606 derived from *Pogostemon cablin* resulted novel metabolites termed as isocochlioquinones D and E (**78**, **79**) and cochlioquinones G and H (**80**, **81**). These metabolites showed cytotoxicity towards tumor cell lines [81]. Endophyte *Fusarium solani* was originated from the roots of *Aponogeton undulatus* Roxb, resulted two cytotoxic compounds, named 7-desmethylscorpinone (**82**) and 7-desmethyl-6-methylbostrycoidin (**83**). *Eurotium rubrum*; an endophyte living on *Suaeda salsa* L., produced rubrumol (**84**). The compound inhibited Top I relaxation activity [82].

3.5. Flavonoids

Flavonoids are phenolic secondary metabolites containing 15 carbon atoms and a heterocyclic ring. They are beneficial nutrients for health and treatment of different disorders.

Kaempferol (**85**) has been obtained from endophytic fungi *Mucor fragilis* collected from rhizomes of *Sinopodophyllum hexandrum* [83]. Luteolin (**86**) from endophyte *Aspergillus fumigatus* of *Cajanus cajan* displayed remarkable antioxidant activity [84]. Two new flavonoids, 7-methoxy-3,3',4',6-tetrahydroxyflavone (**87**) and 2',7-dihydroxy-4',5'-dimethoxyisoflavone (**88**) with one known compound fisetin (**89**) were produced by *Streptomyces* sp. BT01 isolated from root tissues of *Boesenbergia rotunda* [85]. Apigenin (4', 5, 7-trihydroxyflavone) (**90**) has also been reported to be produced by *Chaetomium globosum* from the roots of *C. cajan* [86].

Three secondary metabolites, silybin A (**91**), silybin B (**92**), and isosilybin A (**93**) were reported for the first time

from *Aspergillus iizukae* cultured from *S. marianum* leaves [87]. Naringenin (94) having antioxidant and neuroprotective effect was detected in the extract of the endophytic fungus *Verticillium* sp. isolated from *Lippia sidoides* Cham [88]. Quercetin (95) was predicted in four endophytic bacterial strains of Kenikir leaves. It has shown anticancer, antibacterial and antifungal activities due to its toxicity [89].

3.6. Peptides

Peptides consist of two or more α -amino acids linked in a chain; the carboxyl group of each acid being joined to the amino group of the next by a bond of the type -OC-NH. Bioactive peptides have demonstrated potential for application as health promoting agents. Endophytic fungus of *Castaniopsis fissa* produced cyclo-(L-Val-L-Leu-L-Val-L-Leu) (96) and cyclo-(L-Leu-L-Ala-L-Leu-L-Ala) (97) [90,91]. The compounds showed anticancer properties. Further, curvularides A-E (98-102) were isolated from *Curvularia geniculata* originated from *Catunaregam tomentosa* [92]. For the first time, cycloaspetide A (103) was obtained from *Penicillium janczewskii* K. M. Zalesky collected from *Prumnopitys andina*. The compound was less toxic against human lungs fibroblasts [93].

Trichomides A (104) and B (105) are two new cyclodepsipeptides isolated from the fungus *Trichothecium roseum* IFB-E066, which dwells in the roots of *Imperata cylindrical*. Trichomide A proved to have immunosuppressive effect [94]. Endophyte *Penicillium* sp. of *Acrostichum aureum* origin resulted two new antibacterial compounds named cyclo (Pro-Thr) (106) and cyclo (Pro-Tyr) (107) [95].

3.7. Phenols and Phenolic Acids

Phenol, also known as carboic acid, is an aromatic organic compound with the molecular formula C_6H_5OH . They are sometime called phenolics and contribute many benefits to human health.

A novel phenolic compound, 4-(2,4,7-trioxa-bicyclo [4.1.0] heptan-3-yl) (108) with antifungal and antibacterial activity, was isolated from *Pestalotiopsis mangiferae*, an

endophytic fungus of *Mangifera indica* Linn. [96]. Isolation of an antioxidant compound; graphis lactone A (109) was carried out from *Cephalosporium* sp. IFB-E001 hosted by *Trachelospermum jasminoides*, [97]. A compound, 2-methoxy-4-hydroxy-6-methoxymethyl-benzaldehyde (110) was isolated from *Pezicula* sp. strain 553 residing on coniferous trees [98]. Three phenolic compounds, *p*-hydroxyphenylacetic acid (111), tyrosol (112) and protocatechuic (113) acid were isolated from endophytic fungi *Pseudofusicoccum* sp. derived from *Annona muricata*. All these compounds exhibited antioxidant activities [99]. Pestalachlorides A-C (114-116) as new chlorinated benzophenone derivatives isolated from a plant endophyte *Pestalotiopsis adusta*. Compounds A and B demonstrated significant antifungal activities [100]. A new antimicrobial tridepside colletotric acid (117) was produced by *Colletotrichum gloeosporioides* cultured from *Artemisia mongolica* [11]. A new cytotoxic benzophenone derivative, tenllone I (118) was isolated from the endophytic fungus *Diaporthe li-thocarpus* A740 of *Morinda officinalis* [76].

3.8. Aliphatic Compounds

Those organic compounds whose carbon atoms are linked in open chains, either straight or branched, rather than containing a benzene ring, are known as aliphatic compounds.

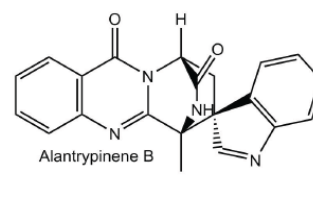
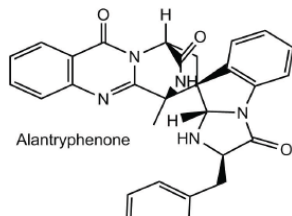
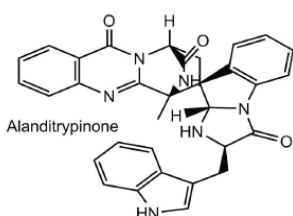
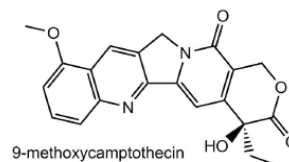
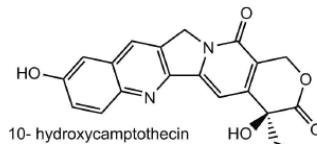
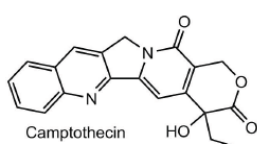
An antimicrobial compound, brefeldin A (119) was obtained from an endophytic fungi *Cladosporium* sp. residing in *Quercus variabilis* [101]. New cyclohexanone derivatives, pestalofones A-E (120-124) were obtained from *Pestalotiopsis fici*, an endophyte fungus inhabitant of the branches of an unidentified tree in Hangzhou, China [102]. Gamahonolides A (125) and B (126) were isolated from *E. typhina* living on *Phleum pretense* [103]. A new 6-hydroxyphomodiol (127) metabolite was characterized from an endophytic *Phomopsis* sp. xz-01 isolated from *Camptotheca acuminata*. The compound showed selective activity against HepG2 cancer cell lines [104]. A novel azaphilone derivative, chaetomugilin D (128) was derived from *C. globosum* that resides on *Ginkgo biloba*. The compound proved to cause significant growth inhibition of brine shrimp and *Mucor miehei* [55].

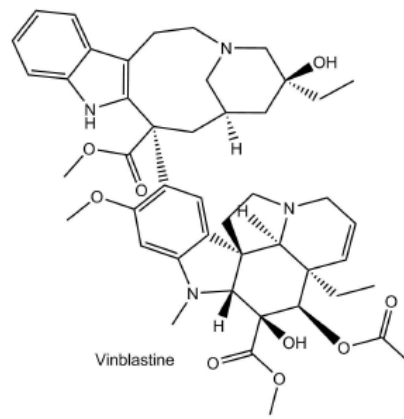
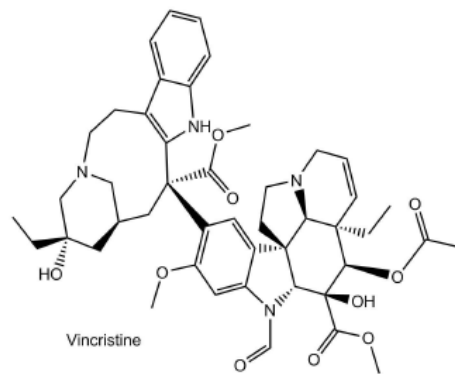
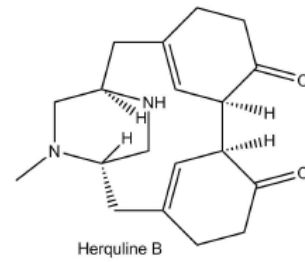
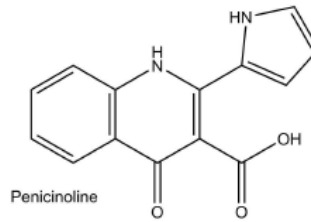
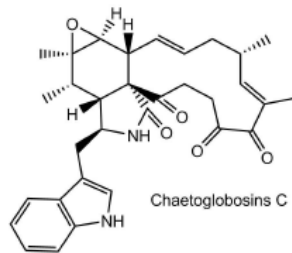
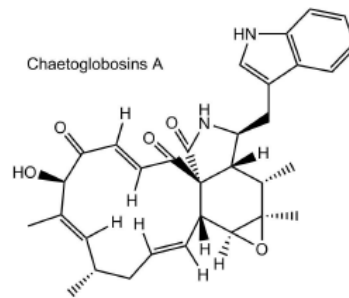
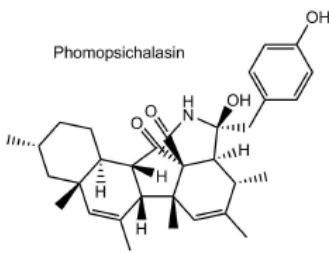
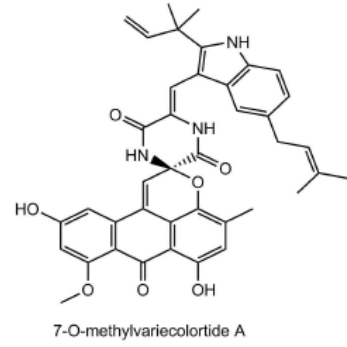
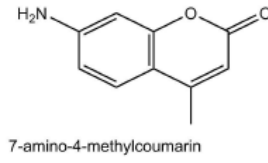
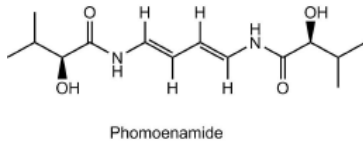
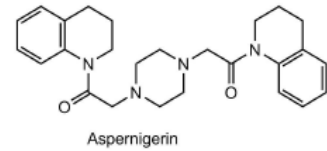
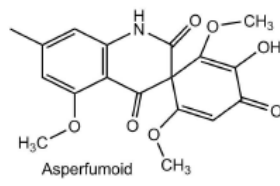
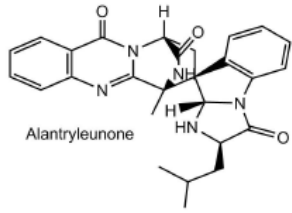
Table 1. SECONDARY METABOLITES OF PLANT ENDOPHYTES AND THEIR PHARMACOLOGICAL ACTIVITIES

No.	Compound Name	Source of origin	Bioactivities	References
Alkaloids				
1	Camptothecin	<i>F. solani</i>	Anticancer	[45,46]
2	10-hydroxycamptothecin	<i>F. solani</i>	Antitumor	[47]
3	9-methoxycamptothecin	<i>F. solani</i>	anticancer	[47]
4	Alanditrypinone	<i>Eupenicillium</i> sp.		[48]
5	Alantryphenone	<i>Eupenicillium</i> sp.		[48]
6	Alantrypinene B	<i>Eupenicillium</i> sp.		[48]
7	Alantryleunone	<i>Eupenicillium</i> sp.		[48]
8	Asperfumoid	<i>A. fumigatus</i> CY018	Antifungal	[49]
9	Aspernigerin	<i>A. niger</i> IFB-E003	Antitumor	[50]
10	Phomoenamamide	<i>Phomopsis</i> sp. PUS-D15	Antibacterial	[51]
11	7-amino-4-methylcoumarin	<i>Xylaria</i> sp.	Antibacterial, antifungal	[52]
12	7-O-methylvariecolortide A	<i>E. rubrum</i>		[53]
13	Phomopsichalasin,	<i>Phomopsis</i>	Antibacterial, antifungal	[54]
14	Chaetoglobosin A	<i>C. globosum</i>	Antibacterial	[55]
15	Chaetoglobosin C	<i>C. globosum</i>	Antibacterial	[56]
16	Cinchonine	<i>Cladosporium</i> CLJ-2		[56]
17	Herquiline B	<i>T. pinophilus</i>	Antimicrobial	[57]
18	Vincristine	<i>Penicillium</i> sp.-VE89L	Anticancer	[58]
19	Vinblastine	<i>Penicillium</i> sp.-VE89L	Anticancer	[58]

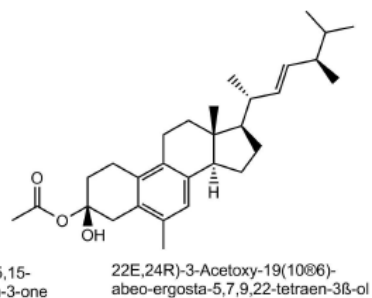
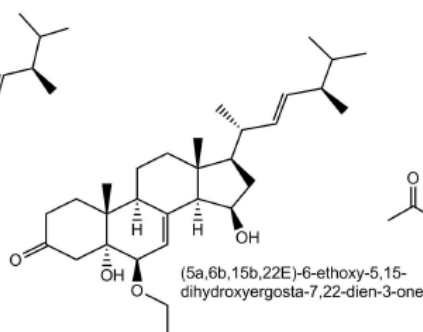
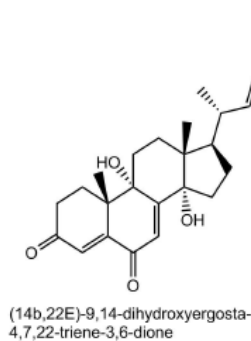
No.	Compound Name	Source of origin	Bioactivities	References
Steroids				
20	(14 β ,22E)-9,14-dihydroxyergosta-4,7,22-triene-3,6-dione	<i>Phomopsis</i>	Antifungal	[60]
21	(5 α ,6 β ,15 β ,22E)-6-ethoxy-5,15-dihydroxyergosta-7,22-dien-3-one	<i>Phomopsis</i>	Antifungal	[60]
22	(22E, 24R)-3-acetoxy-19(10 \rightarrow 6)-abeo-ergosta-5,7,9,22-tetraen-3 β -ol	<i>Colletotrichum</i> sp.	Antibacterial	[61]
23	3 β , 5 α -dihydroxy-6 β -acetoxyergosta-7, 22-diene	<i>Colletotrichum</i> sp.	Antifungal	[62]
24	3 β , 5 α -dihydroxy-6 β -phenyl- acetyloxyergosta-7, 22-diene	<i>Colletotrichum</i> sp.	Antifungal	[62]
25	Globosterol	<i>C. globosum</i> ZY-22		[63]
26	Tetrahydroxylated ergosterol (22E, 24R)-ergosta-7,22-diene-3 β ,5 α ,6 β , 9 α -tetraol	<i>C. globosum</i> ZY-22		[63]
27	5 α , 8 α -epidioxyergosterol	<i>Nodulisporium</i> sp.		[64]
28	Solanioic acid	<i>R. solani</i>	Antibacterial	[65]
29	Fusaristerol B	<i>Fusarium</i> sp.	Antiinflammatory	[66]
30	Fusaristerol C	<i>Fusarium</i> sp.	Antiinflammatory	[66]
31	Fusaristerol D	<i>Fusarium</i> sp.	Antiinflammatory	[66]
Terpenoids				
32	Xylarenone A	<i>Xylaria</i> sp. NCY2	Antitumor	[67]
33	Xylarenone B	<i>Xylaria</i> sp. NCY2	Antitumor	[67]
34	Xylarenic acid	<i>Xylaria</i> sp. NCY2	Antitumor	[67]
35	(7S, 9S, 10S)-3, 9, 12-trihydroxycalamenene,	<i>P. cassiae</i>	Antifungal	[68]
36	(7S, 9R, 10S)-3, 9, 12-trihydroxycalamenene	<i>P. cassiae</i>	Antifungal	[68]
37	3, 12 dihydroxycalamenene	<i>P. cassiae</i>	Antifungal	[68]
38	3, 12-dihydroxycadalene	<i>P. cassiae</i>	Antifungal	[68]
39	3, 11, 12-trihydroxycadalene	<i>P. cassiae</i>	Antifungal	[68]
40	Botryosphaerin A	<i>Botryosphaeria</i> sp. MHF		[69]
41	Botryosphaerin B	<i>Botryosphaeria</i> sp. MHF		[69]
42	Botryosphaerin C	<i>Botryosphaeria</i> sp. MHF		[69]
43	Botryosphaerin D	<i>Botryosphaeria</i> sp. MHF		[69]
44	Botryosphaerin E	<i>Botryosphaeria</i> sp. MHF		[69]
45	Acrostalidic acid	<i>Botryosphaeria</i> sp. MHF		[69]
46	Acrostalic acid	<i>Botryosphaeria</i> sp. MHF		[69]
47	Agathic acid	<i>Botryosphaeria</i> sp. MHF		[69]
48	Isocupressic acid	<i>Botryosphaeria</i> sp. MHF		[69]
49	Xylaroside A	<i>Xylaria</i> sp. PSU-D14	Antifungal	[70]
50	Xylaroside B	<i>Xylaria</i> sp. PSU-D14	Antifungal	[70]
51	Scopararane A	<i>E. scoparia</i> PSU-D44	Antimicrobial	[71]
52	Scopararane B	<i>E. scoparia</i> PSU-D44	Antimicrobial	[71]
53	Diaporthein A	<i>E. scoparia</i> PSU-D44	Antimicrobial	[71]
54	Diaporthein B	<i>E. scoparia</i> PSU-D44	Antimicrobial	[71]
55	Dihydroxysabinane	<i>Phomopsis</i> sp. XZ-26		[72]
56	Preaustinoid B2	<i>Penicillium</i> sp.		[73]
57	Preaustinoid A3	<i>Penicillium</i> sp.		[73]
58	Austinolide	<i>Penicillium</i> sp.		[73]
59	Isoaustinone	<i>Penicillium</i> sp.		[73]
60	Preaustinoid A1	<i>P. brasilianum</i>		[74]
61	Preaustinoid A2	<i>P. brasilianum</i>		[74]
62	Preaustinoid B1	<i>P. brasilianum</i>		[74]
63	Guanacastepene A	CR115	Antibacterial	[75]
64	Guanacastepene	CR115	Antibacterial	[75]
65	Periconicin A	<i>Periconia</i> sp.	Antibacterial	[75]
66	Periconicin B	<i>Periconia</i> sp.	Antibacterial	[75]
67	Lithocarin B	<i>D. lithocarpus</i> A740	Antitumor	[76]
68	Lithocarin C	<i>D. lithocarpus</i> A740	Antitumor	[76]
69	Lithocarin D	<i>D. lithocarpus</i> A740		[76]
Quinones				
70	Herbarin	<i>D. nanum</i>	Antiinflammatory, antidiabetic	[77]
71	Herbaridine A	<i>D. nanum</i>		[77]
72	Preussomerin J	<i>Mycelia sterile</i>	Antibacterial, antifungal	[78]
73	Preussomerin K	<i>Mycelia sterile</i>	Antibacterial, antifungal	[78]
74	Preussomerin L	<i>Mycelia sterile</i>	Antibacterial, antifungal	[78]
75	3-O-methylalaternin	<i>Ampelomyces</i> sp.	Antibacterial	[79]
76	Altersolanol A	<i>Ampelomyces</i> sp.	Antibacterial	[79]
77	4-dehydroxyaltersolanol A	<i>N. oryzae</i>	Anticancer	[80]
78	Isocochlioquinone D	<i>B. sorokiniana</i> A606	Antitumor	[81]
79	Isocochlioquinone E	<i>B. sorokiniana</i> A606	Antitumor	[81]
80	Cochlioquinone G	<i>B. sorokiniana</i> A606	Antitumor	[81]
81	Cochlioquinone H	<i>B. sorokiniana</i> A606	Antitumor	[81]
82	7-desmethylscorpinone	<i>F. solani</i>	Anticancer	[82]
83	7-desmethyl-6-methylbostrycoidin	<i>F. solani</i>	Anticancer	[82]
84	Rubrumol	<i>E. rubrum</i>	Top 1 relaxation activity inhibitor	[82]

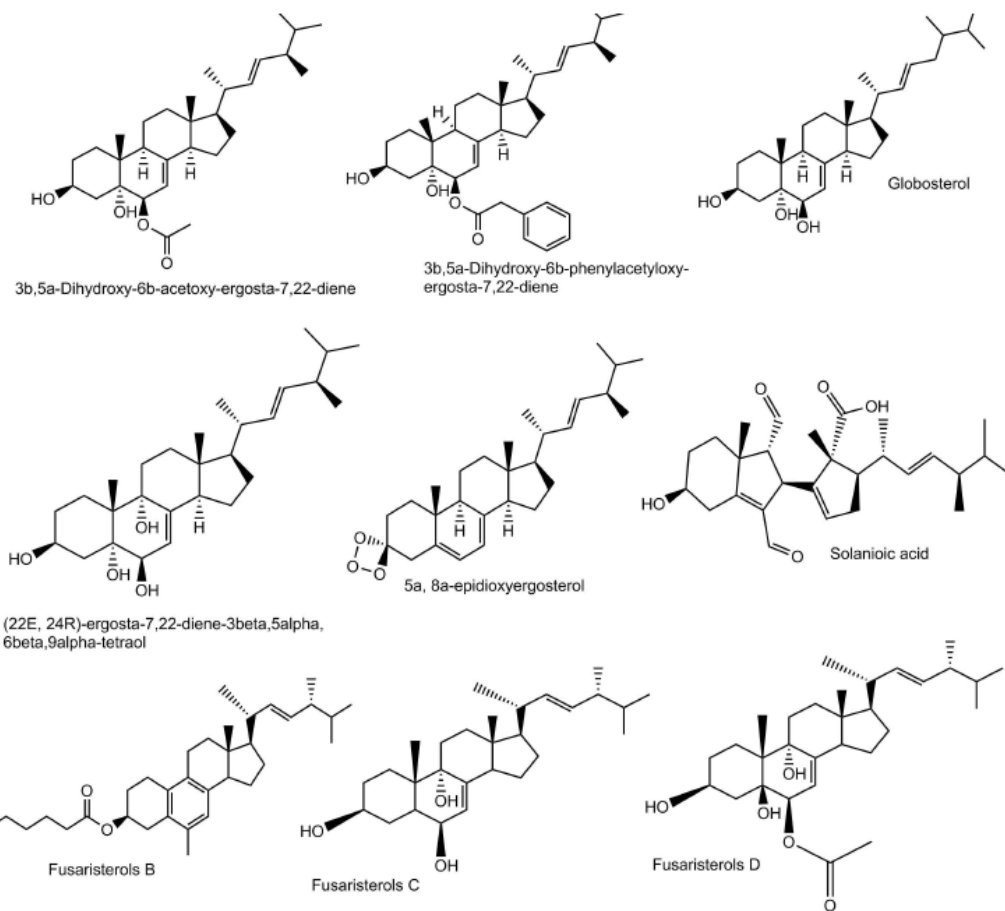
No.	Compound Name	Source of origin	Bioactivities	References
Flavonoids				
85	Kaempferol	<i>M. fragilis</i>	Anticancer, antiinflammatory	[83]
86	Luteolin	<i>A. fumigatus</i>	Antioxidant	[84]
87	7-methoxy-3,3',4',6-tetrahydroxyflavone	<i>Streptomyces</i> sp. BT01	Antibacterial	[85]
88	2',7-dihydroxy-4',5'-dimethoxyisoflavone	<i>Streptomyces</i> sp. BT01	Antibacterial	[85]
89	Fisetin	<i>Streptomyces</i> sp. BT01	Antibacterial	[85]
90	Apigenin	<i>C. globosum</i>	Antioxidant	[86]
91	Silybin A	<i>A. iizukae</i>	Anticancer, antibacterial	[87]
92	Silybin B	<i>A. iizukae</i>	Anticancer	[87]
93	Isosilybin A	<i>A. iizukae</i>	Anticancer	[87]
94	Naringenin	<i>Verticillium</i> sp.	Antioxidant, neuroprotective	[88]
95	Quercetin	<i>Serratia</i> sp., <i>Neisseria</i> sp., <i>Acinetobacter</i> sp., <i>Yersinia</i> sp.	Antibacterial, antifungal, anticancer	[89]
Peptides				
96	Cyclo-(L-Val-L-Leu-L-Val-L-Leu)	<i>C. fissa</i>	Anticancer	[90,91]
97	Cyclo-(L-Leu-L-Ala-L-Leu-L-Ala)	<i>C. fissa</i>	Anticancer	[90,91]
98	Curvularide A	<i>C. geniculata</i>		[92]
99	Curvularide B	<i>C. geniculata</i>	Antifungal	[92]
100	Curvularide C	<i>C. geniculata</i>		[92]
101	Curvularide D	<i>C. geniculata</i>		[92]
102	Curvularide E	<i>C. geniculata</i>		[92]
103	Cycloaspetide A	<i>P. janczewskii</i> K. M. Zalesky	Cytotoxic against human lung fibroblasts	[93]
104	Trichomide A	<i>T. roseum</i> IFB-E066	Immunosuppressant	[94]
105	Trichomide B	<i>T. roseum</i> IFB-E066	Immunosuppressant	[94]
106	Cyclo (Pro-Thr)	<i>Penicillium</i> sp.	Antibacterial	[95]
107	Cyclo (Pro-Tyr)	<i>Penicillium</i> sp.	Antibacterial	[95]
Phenols and Phenolic Acids				
108	4-(2, 4, 7-trioxa-bicyclo [4.1.0] heptan-3-yl)	<i>P. mangiferae</i>	Antifungal, antibacterial	[96]
109	Graphisactone A	<i>Cephalosporium</i> sp. IFB-E001	Antioxidant	[97]
110	2-Methoxy-4-hydroxy-6-methoxymethyl-benzaldehyde	<i>Pezicula</i> sp. strain 553	Antifungal, antibacterial	[98]
111	<i>p</i> -hydroxyphenylacetic acid	<i>Pseudofusicocum</i> sp.	Antibacterial, antioxidant	[99]
112	Tyrosol	<i>Pseudofusicocum</i> sp.	Antioxidant	[99]
113	Protocatechuic acid	<i>Pseudofusicocum</i> sp.	Antioxidant	[99]
114	Pestalachloride A	<i>P. adusta</i>	Antifungal	[100]
115	Pestalachloride B	<i>P. adusta</i>	Antifungal	[100]
116	Pestalachloride C	<i>P. adusta</i>		[100]
117	Colletotric acid	<i>C. gloeosporioides</i>	Antimicrobial	[11]
118	Tenllone I	<i>D. li-thocarpus</i> A740		[76]
Aliphatic Compounds				
119	Brefeldin A	<i>Cladosporium</i> sp.	Antitumor, antifungal, antiviral	[101]
120	Pestalofone A	<i>P. fici</i>	Antiviral	[102]
121	Pestalofone B	<i>P. fici</i>	Antiviral	[102]
122	Pestalofone C	<i>P. fici</i>	Antifungal	[102]
123	Pestalofone D	<i>P. fici</i>		[102]
124	Pestalofone E	<i>P. fici</i>	Antiviral, antifungal	[102]
125	Gamahonolide A	<i>E. typhina</i>	Antifungal	[103]
126	Gamahonolide B	<i>E. typhina</i>		[103]
127	6-hydroxyphomodiol	<i>Phomopsis</i> sp. xz-01	Anticancer	[104]
128	Chaetomugilin D	<i>C. globosum</i>	Antifungal, brine shrimp growth inhibition	[55]

Alkaloids:

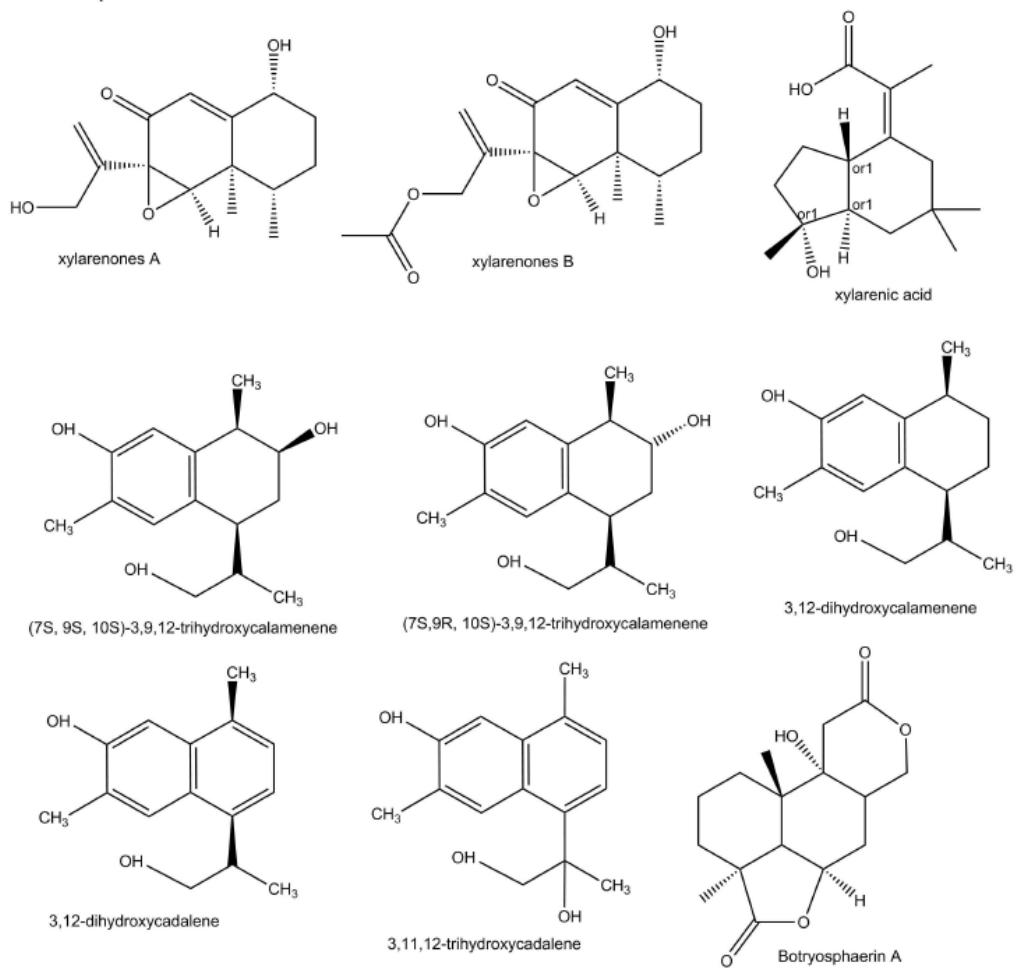


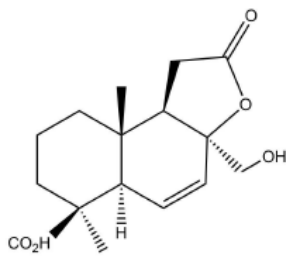
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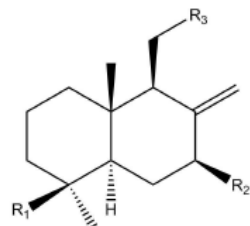


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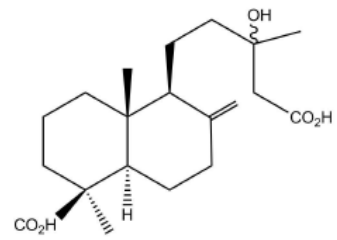


Botryosphaerin B

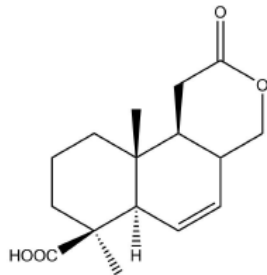


Botryosphaeri

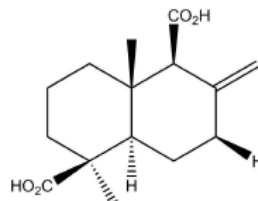
C: $R_1 = \text{CO}_2\text{H}$, $R_2 = \text{H}$, $R_3 = \text{HOCH}_2$
 D: $R_1 = \text{HOCH}_2$, $R_2 = \text{H}$, $R_3 = \text{CO}_2\text{H}$



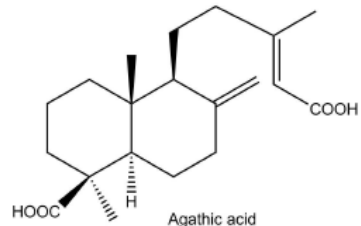
Botryosphaerin E



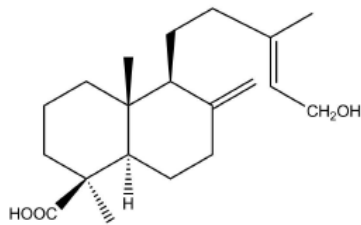
Acrostalidic acid



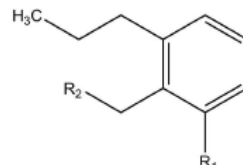
Acrostalic acid



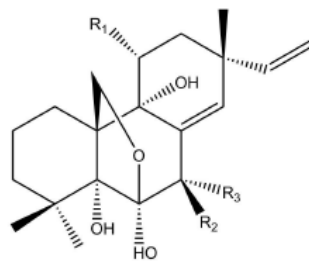
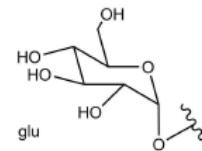
Agathic acid



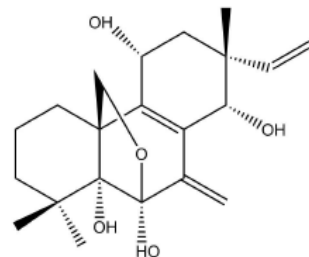
Isocupressic acid



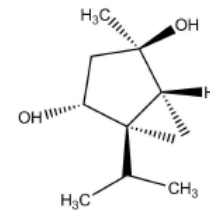
Xylaroside A: $R_1 = \text{OH}$, $R_2 = \text{glu}$
 Xylarosides B: $R_1 = \text{glu}$, $R_2 = \text{OH}$



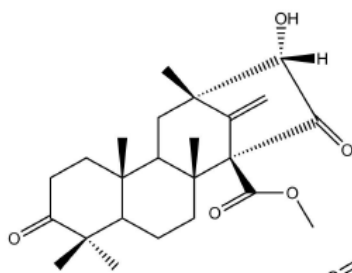
Scoparane A: $R_1 = \text{H}$, $R_2 + R_3 = \text{O}$
 Diaporthein A: $R_1 = \text{OH}$, $R_2 = \text{H}$, $R_3 = \text{OH}$
 Diaporthein B: $R_1 = \text{OH}$, $R_2 + R_3 = \text{O}$



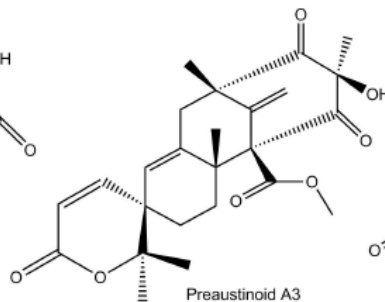
Scoparane B



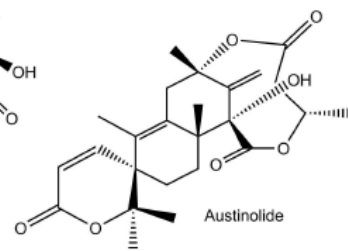
Monoterpene dihydroxysabinane



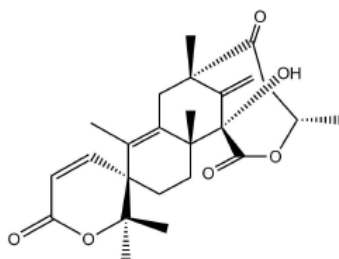
Preaustinoid B2



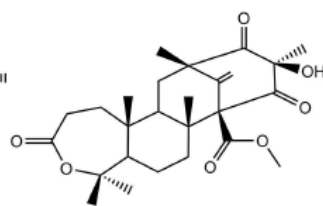
Preaustinoid A3



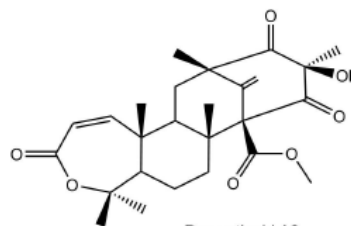
Austinolide



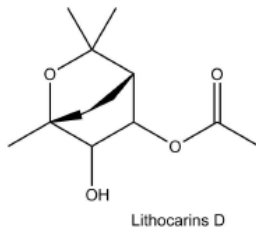
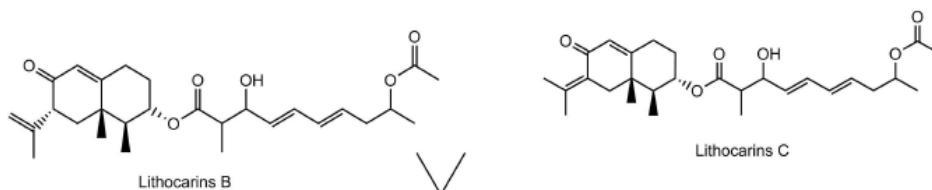
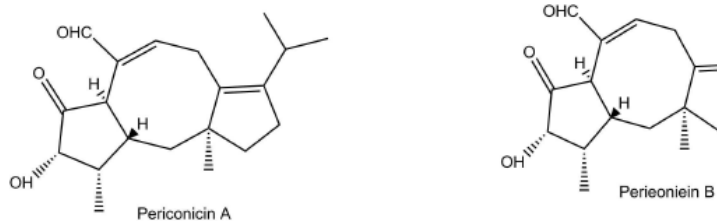
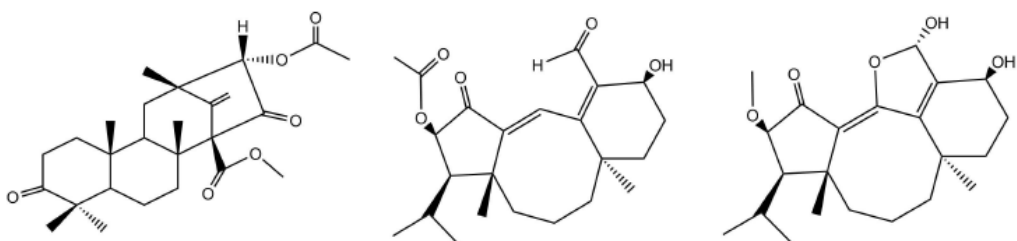
Isoaustinone



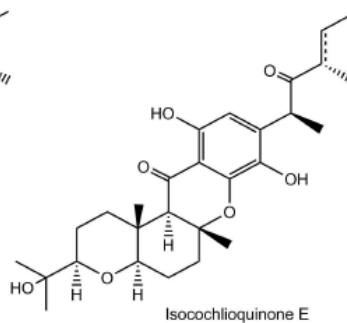
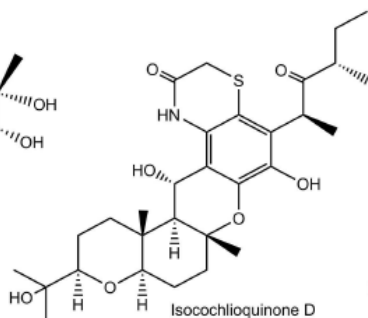
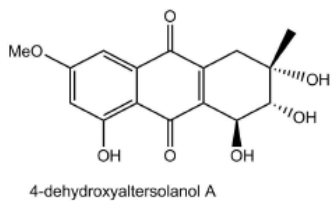
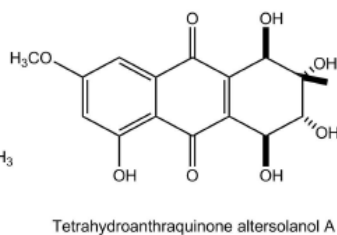
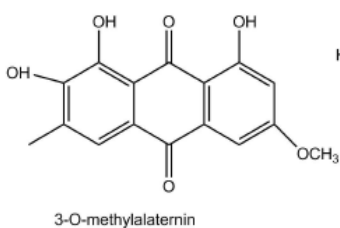
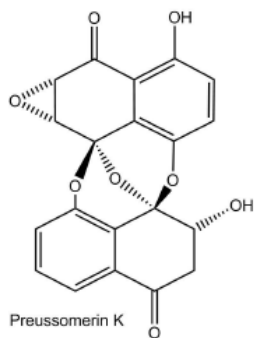
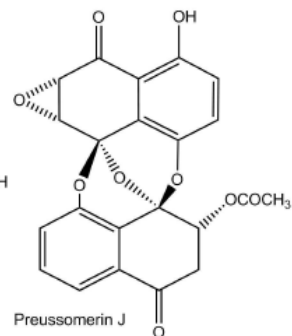
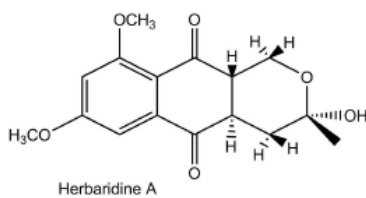
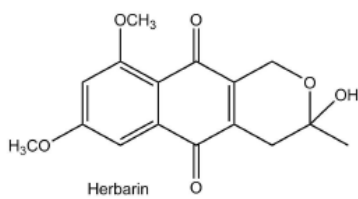
Preaustinoid A1

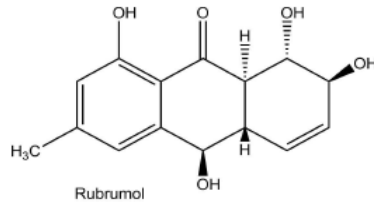
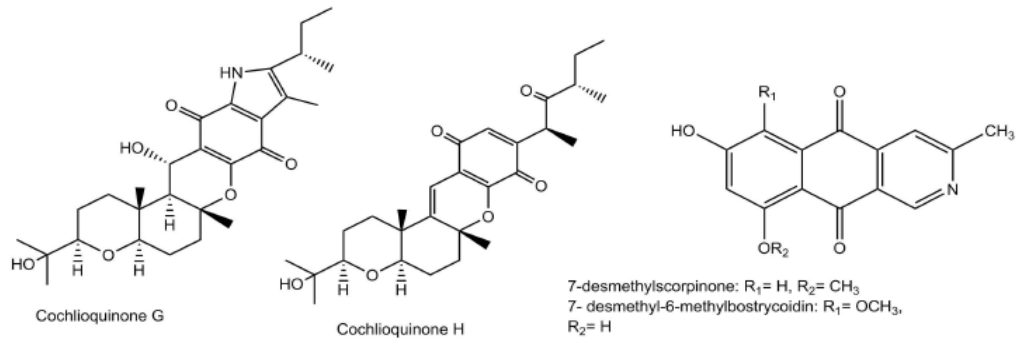


Preaustinoid A2

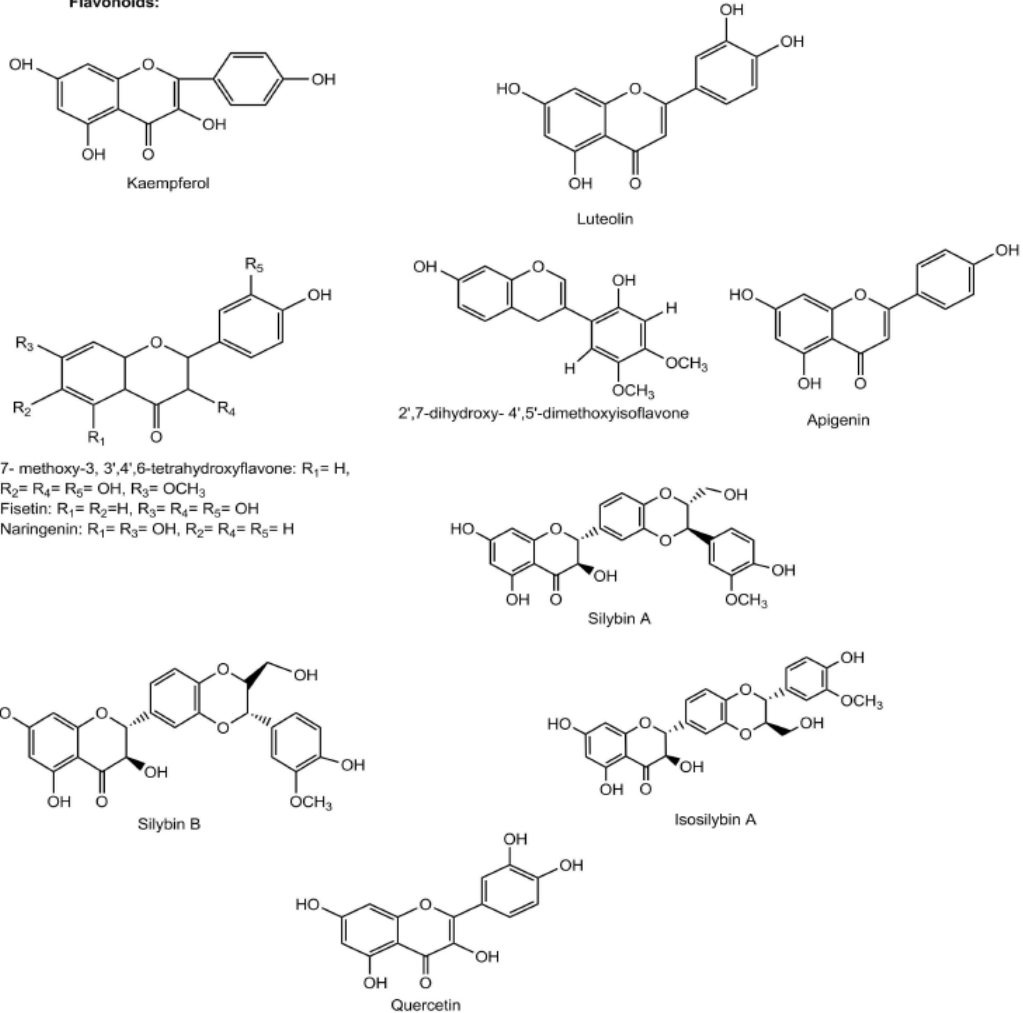


Quinones:

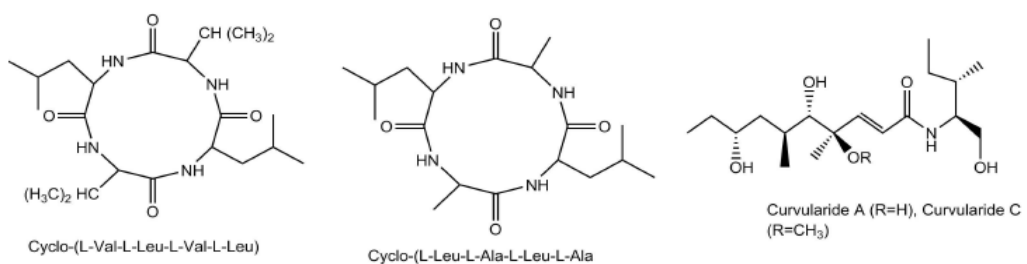


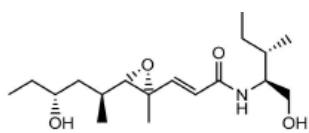


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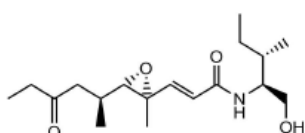


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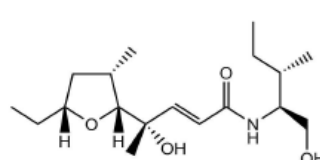




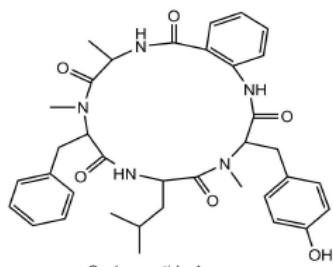
Curvularide B



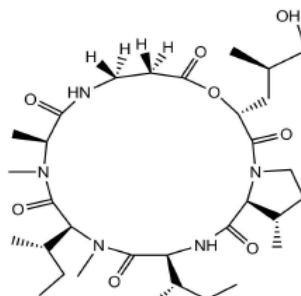
Curvularide D



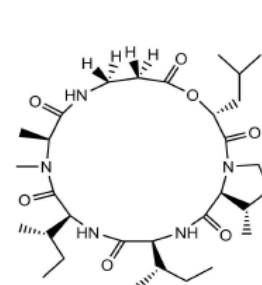
Curvularide E



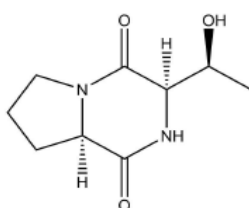
Cycloaspetide A



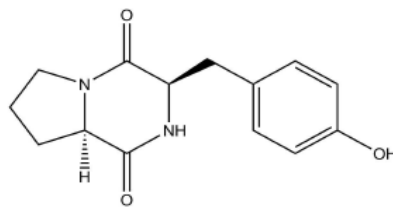
Trichomide A



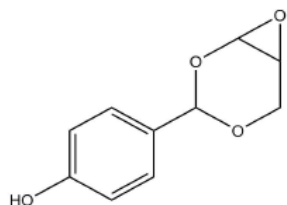
Trichomide B



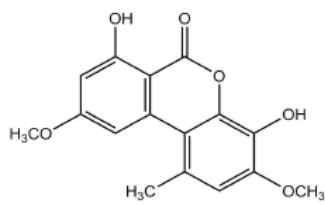
Cyclo- (Pro-Thr)



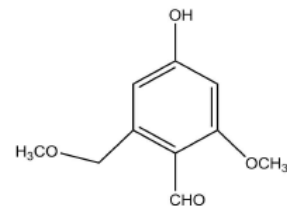
Cyclo- (Pro-Tyr)

Phenols and Phenolic Acids:

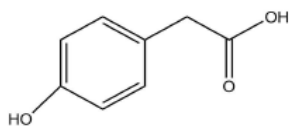
4-(2,4,7-trioxabicyclo[4.1.0]heptan-3-yl)



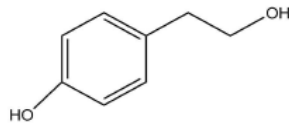
Graphis lactone A



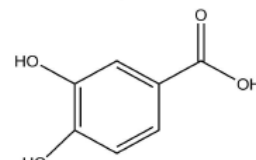
2-Methoxy-4-hydroxy-6-methoxymethylbenzaldehyde



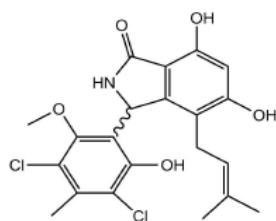
p-hydroxyphenylacetic acid



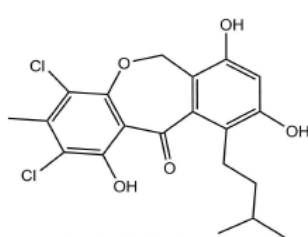
Tyrosol



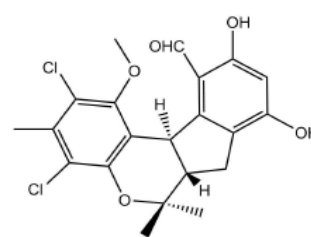
Protocatechuic acid



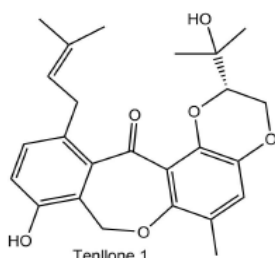
Pestalchloride A



Pestalchloride B

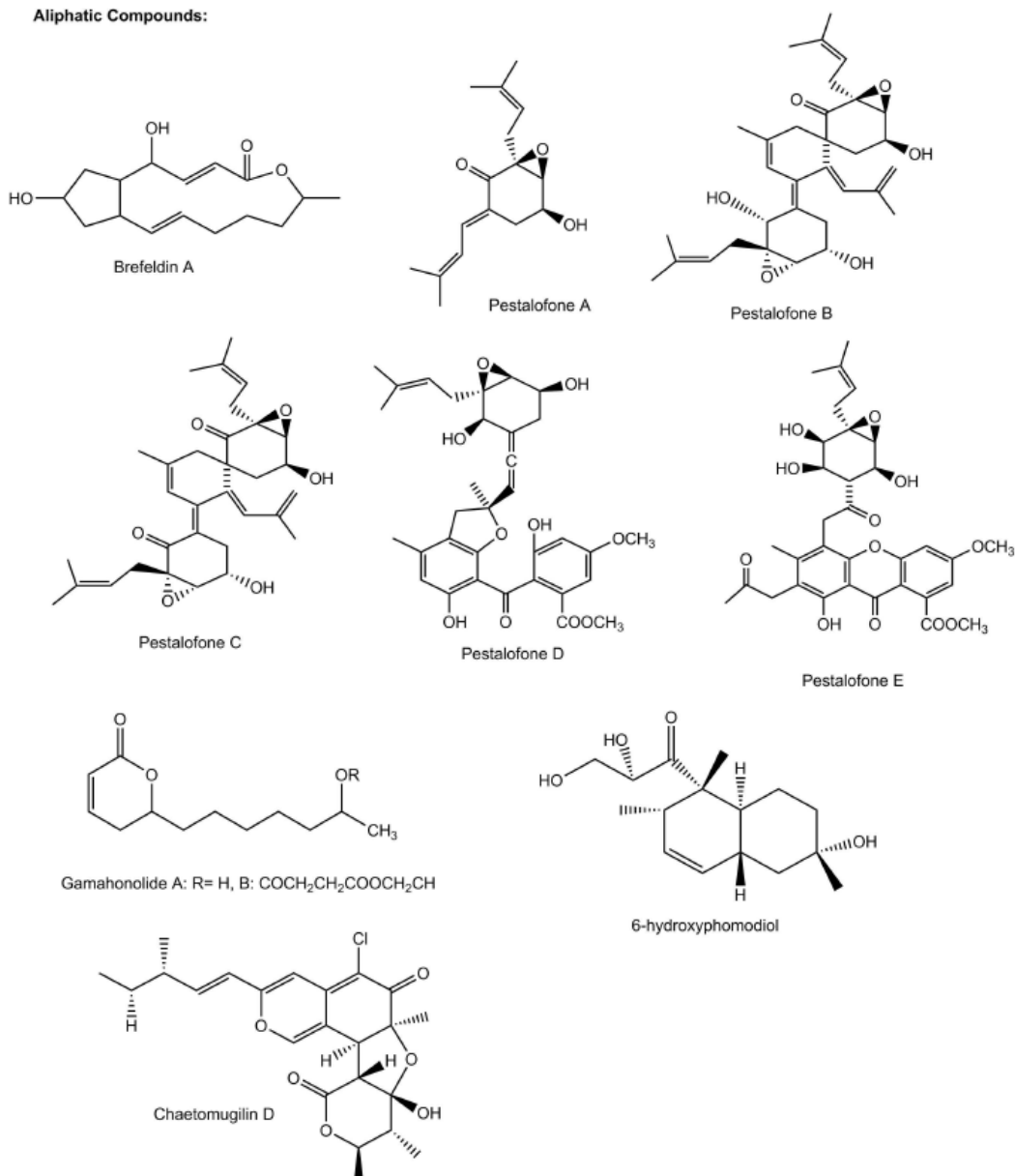


Pestalchloride C



Tenlone 1

Aliphatic Compounds:



4. Conclusion and Future Perspectives

It is evident from the literature and data available about the active metabolites produced by plant endophytes that the field is of great interest for Chemists and Biologists. Biology of endophytic microorganisms has developed as a new arena to hunt for novel compounds. A number of bioactive compounds have been isolated and reported so far. Endophytes are continuously under investigation to report many novel compounds of high biological importance.

The existence behavior of endophytes needs better understanding to select and study relevant plants for microfloral compounds. The progress to find new endophytes like *Muscador albus*, and *Pestalotiopsis microspora*, *Piriformospora indica*, and *Taxomyces andreanae* has made scientists attracted towards new drugs and technological development [105]. Searching for bioactive compounds, based on endophytes would be a possible way to avoid drug resistance of bacterial strains [106]. Hence, new acquisitions in this field will be fundamental in order to exploit microbial strains for highly effective and large-scale production of plant derived drugs [107].

Acknowledgments

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