Pharmacological Applications of Bioactive Secondary Metabolites from Endophytes

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Abstract

Endophytes are reservoirs of new and effective bioactive compounds that generally belong to the classes such as terpenoids and steroids, fatty acid-derived substances and polyketides, alkaloids, nonribosomal polypeptides, and enzyme cofactors. These classes of compounds can be used for antimicrobial, insecticidal, cancer preventive, antioxidant, antiviral, antidiabetic, immunosuppressant, immunostimulant, and several other properties. Endophytes-derived secondary metabolites have tremendous applications in the field of agronomy, medicine, food, and cosmetics. Recent discoveries have shown that microbes associated with plants could be exploited as an important source for the development of new drugs. Finding novel molecules may combat terminal diseases, drug resistance, and other severe challenges related to human health. The newly developed drugs may be an effective contender for the treatment of newly developing diseases in humans as well as animals. This chapter aims to figure out the pharmacological uses of endophytes as a novel source of drugs against several diseases and other promising therapeutic use.

Keywords

Endophytes · Natural compounds · Pharmacological activity · Disease treatment
5.1 Introduction

Bioactive metabolites produced by plants have been used for curing or preventing illness and other distress in humans as well as animals. The microbes associated with the plants are also reported to produce a variety of metabolites that may benefit the plant or help their survival. Most of the plants often provide a unique habitat for the survival and establishment of endophytes (Strobel and Daisy 2003). Generally, endophytes are omnipresent organisms which are found in association with the internal tissues of the plant, at least a part of their life cycle, without causing direct or indirect infections or related symptoms (Strobel and Daisy 2003). Fungi dominate as endophytes usually share a mutualistic relationship with the host plant. But bacterial endophytes are also found associated with plants and produce an array of biologically active secondary metabolites. Endophytic fungi, as well as bacteria, have been recognized as valuable resources for the production of novel biologically active secondary metabolites with tremendous application in the field of medicine, agriculture, food, etc.

Increased demand for the novel and active remedies for treating human conditions is growing. Recent antibiotic resistance issues, life threatening viruses, recurring problems emanated from organ transplant patients, various types of cancers, and other health conditions, etc. underscore the insufficiency of existing medication for the treatment of each medical problem. Here comes the application of endophytes in the field of pharmacology and medicine. Nearly 300,000 plant species have been existing in the earth; each plant is hosting a multitude of fungal as well as bacterial endophytes. In reference to endophytic biology, less than 5% of the plants have been studied for their endophytic diversity. However, the chances to found novel endophytic microorganisms among the multitude of vegetations in various niches and ecosystems are great. Biologically derived compounds or its products have remarkable therapeutic applications, as well as they instigate the development of synthetic methodologies to permit the likelihood of making analogs of innovative lead compounds or products with enhanced pharmaceutical activities. The secondary metabolite discovery and its production from endophytic organisms have materialized as a stirring area of study in biotechnology. A multitude of compounds with immense pharmaceutical importance has been identified and isolated from several endophytic organisms (Strobel and Daisy 2003; Tiwari et al. 2017; Kharwar et al. 2011). This chapter aims to provide an insight into the pharmacologically useful bioactive secondary metabolites produced by endophytic microorganisms.

5.2 Plant–Endophyte Association: Selection of Suitable Plants for Endophyte Isolation and Subsequent Metabolite Studies

The bioactive metabolite production is linked with its host organism and its environmental niche (Mittermeier et al. 1999). It is essential to comprehend the strategies and rationale to provide the finest opportunities to isolate new endophytes as well as
ones producing new bioactive compounds or products. Therefore, the vast diversity of plant communities in the earth makes the researcher adopt creative and imaginative strategies for the selection and processing of endophytes exhibiting desired bioactivity. Studies have shown that microorganisms and their biotopes which are persistently subjected to metabolic and ecological interactions tend to produce even more biologically active secondary metabolites (Schulz et al. 2002). Usually, the selection of plants for the isolation of endophytes is based on four selection strategies described in Fig. 5.1.

5.3 Structural Diversity and Bio-activities of Endophytic Secondary Metabolites

Structurally unique and novel natural compounds from endophytes facilitated the pharmacological application of such compounds and the discovery of novel drugs. Endophytes associated with plants have been reported to synthesize structurally distinct and diverse classes of secondary metabolites. Natural compounds, their synthetic analogs, and synthetic compounds that mimic natural compounds in their biological activities embody most of the accepted or approved small molecule drugs (Newman and Cragg 2016; Patridge et al. 2016). Natural compounds that are biologically active and structurally diverse pharmacophores play a major role in novel drug discovery (Xiao et al. 2016). The biomolecules which are produced by the endophytes are meant for the ecological adaptations and coevolve with the host plant. The functional natural compounds derived from the endophytes are significant in the ecological perspective. For instance, Neotyphodium coenophialum, an endophytic fungus living in the Festuca arundinacea, produces toxic alkaloids that help the host to escape from herbivorous by causing “fescue toxicosis” (Lyons et al. 1986). From the pharmacological perspective, the alkaloid can be used as a therapeutic compound in several diseases. Several endophytes are known to produce an
array of biological compounds. The natural compounds from the endophytes can be
classified based on their biological activities, structures, and their biosynthesis.
Table 5.1 classifies the compounds based on their precursor and further arranged
on their structural features.

5.4 Pharmaceutical Application of Natural Products Obtained
from Endophytes

Endophyte research has provided many potential drugs with promising antimicro-
bial, antioxidant, virus inhibitory, antidiabetic, immunosuppressant activities, etc.
The finding of these compounds gives hope to fighting incurable diseases, antimicro-
bial resistance, and other recent challenges related to medicine and human health.
The following section briefly discusses the natural compounds obtained from endo-
phytic microorganisms (Fig. 5.2) and their potential relevance in the pharmaceutical
industry for the development of medicines or supplements.

5.4.1 Endophytic Products as Antimicrobial and Antiviral Agents

Antimicrobial products are low-molecular-weight compounds that are active against
microbes at lower concentrations. Several micromolecules are reported to have
antimicrobial activity against a vast range of diseases causing bacteria, fungi,
viruses, and protozoans. A unique antymycotic peptide cryptocandin was isolated
from a fungus Pezicula cinnamomea, associated with the hardwood Tripterigeum
wilfordii found in Europe. The plant was used as a traditional medicine in Eurasia
(Strobel and Daisy 2003). This natural bioactive compound is related to pneumocandins and echinocandins, used to known as antymycotics (Singh et al.
2013). Cryptocandin-related antymycotic compounds are also produced by Pezicula
cinnamomea and are active against several pathogenic fungi in plants such as
Botrytis cinerea and Sclerotinia sclerotiorum. The endophytic compound is being
used as an antymycotic agent against skin and nails fungal diseases (Onishi et al.
2000; Miller et al. 1998).

Pseudomonas viridiflava is a fluorescent bacteria associated with the internal
tissues of many grass species. The bacteria produce ecomycins, natural lipopeptides
with a molecular mass ranges from 1153 to 1181. The compounds are used against
disease causing fungi Cryptococcus neoformans and Candida albicans (Miller et al.
1998). Another plant-associated bacteria Pseudomonas spp. produce a novel
lipopeptide family compound known as pseudomucins and is active against Candida
albicans, Cryptococcus neoformans, and several plant-pathogenic fungi such as
Ceratocystis ulmi and Mycosphaerella fijiensis (Ballio et al. 1994; Harrison et al.
1991).

An endophytic fungi Pestalotiopsis microspora isolated from different plant
sources produce an array of bioactive compounds, viz. antifungal ambic acid
(endophytic rain forest fungi) (Li et al. 2001), terrain (Harper et al. 2001), pestaloside
Table 5.1 Classification of major bioactive compounds produced by endophytes based on their precursor molecule/chemical classes

| Precursor molecule/chemical class | Pharmacological activity                                                                 | Endophytic organism       | Host plant                      | Reference(s)                  |
|----------------------------------|------------------------------------------------------------------------------------------|---------------------------|---------------------------------|------------------------------|
| **Polyketides**                  |                                                                                          |                           |                                 |                              |
| Macrolides                       |                                                                                          |                           |                                 |                              |
| Divergolides                     | Antibacterial activity against *Mycobacterium vaccae*, *Bacillus subtilis* and *Staphylococcus aureus* and cytotoxic properties against lung cancer cell lines | *Streptomyces* sp.        | Mangrove                        | Ding et al. (2011), Xu et al. (2011) |
| Actinoallolides                  | Anti-trypanosomal and used for treating Chagas disease                                    | *Actinoallomurus fulvus*  | Roots of *Capsicum frutescens*  | Inahashi et al. (2015)        |
| **Benzopyran**                   |                                                                                          |                           |                                 |                              |
| Chromanones                      |                                                                                          |                           |                                 |                              |
| Blennolides                      | Antifungal and antibacterial activities against *Microbotryum violaceum* and *Bacillus megaterium* and *Escherichia coli*. Antialgal activity against *Chlorella fusca* | *Blennorida* sp.          | *Carpobroyus edulis* found in canary island | Zhang et al. (2008)          |
| Microsphaeropsones               | Antibacterial, fungicidal, and algicidal properties                                       | *Microsphaeropsis* sp.    | *Crepidomanes intricatum*      | Krohn et al. (2009)           |
| Isofusidienols                   | Antifungal activity against *Candida albicans* and antibacterial activity against gram-positive and gram-negative bacteria | *Chalara* sp.             | *Artemisia vulgaris*            | Lösgen et al. (2008)          |
| Lycopodiellactone                | Not reported                                                                              | *Paraphaeosphaeria neglecta* | Hawaiian indigenous plant, *Lycopodiella cernua* | Li et al. (2015)             |
| **Spiro compounds**              |                                                                                          |                           |                                 |                              |
| Virgatoloids                     | Antimicrobial activity against plant fungal pathogens                                     | *Pestalotiopsis virgatula*| Bark of *Terminalia chebula*    | Kesting et al. 2009          |
| Spiro-mamakone                   | Cytotoxicity toward the P388 murine leukemia cell line and antibacterial activity          | Non-sporulating endophytic fungus (unidentified) | *Knightia excels*              | Van Der Sar et al. (2006)    |

(continued)
| Precursor molecule/chemical class | Pharmacological activity | Endophytic organism | Host plant | Reference(s) |
|----------------------------------|--------------------------|---------------------|------------|--------------|
| Penicillactones                  | Active in inhibiting the release of β-glucuronidase from polymorphonuclear leukocytes | *Penicillium dangeardii* | *Lysidice rhodostegia* | Liu et al. (2013) |
| **Quinones**                     |                          |                     |            |              |
| Torreyanic acid                  | Cytotoxic agent, caused cell death by apoptosis | *Pestalotiopsis microspora* | *Torreya taxifolia* | Lee et al. (1996) |
| **Nitrogen-containing heterocycles** |                          |                     |            |              |
| Chaetoglobins                    | Cytotoxic against the human breast cancer cell line MCF-7 and colon cancer cell line SW1116 | *Chaetomium globosum* | *Imperata cylindrical* | Ding et al. (2006) |
| Alternar lactam                  | Effective against human cervix HeLa adenocarcinoma cell and human hepatocellular carcinoma | *Alternaria sp.* | *Leaves of Carex aridula* | Zhang et al. (2010) |
| **Noribosomal peptides**         |                          |                     |            |              |
| Aspertryptanthrins               | Not reported             | *Aspergillus sp.*   | *Melia azedarach L.* | Lhamo et al. (2015) |
| Spirobrocazines                  | Antibacterial activities against *E. coli, Staphylococcus aureus* and *Vibrio harveyi* | *Penicillium brocae* | *Mangrove* | Meng et al. (2016) |
| Neosartoryadins                  | Inhibitory effects against influenza A virus (H1N1) | *Neosartorya udagawae* | *Mangrove* | Yu et al. (2016) |
| Chaetominine                     | Anti-tumor (human leukemia K562 and colon cancer SW1116 cell lines) | *Chaetomium sp.* | *Adenophora axilliflora* | Jiao et al. (2006) |
| Apicidins                        | Antiprotozoal activities by reversibly inhibiting histone deacetylase (HDAC) and anti-tumor effects | *Fusarium pallidoroseum* | *Mangrove* | Darkin-Rattray et al. (1996) |
| **Isoprenoids**                  |                          |                     |            |              |
| **Steroids**                     |                          |                     |            |              |
| Solanic acid                     | Inhibitory activities against *Bacillus subtilis, S. aureus,* and methicillin-resistant *S. aureus* | *Rhizoctonia solani* | *Cyperus rotundus* | Ratnaweera et al. (2015) |
| Secondary Metabolites          | Pharmacological Activity                                                                 | Secondary Metabolites          | Literature Reference               |
|-------------------------------|------------------------------------------------------------------------------------------|-------------------------------|-----------------------------------|
| Asterogynins                  | (MRSA), antifungal activity against *Candida albicans*                                   | Chalara alabamensis           | Asterogyne martiana               |
| Wortmannines, secovironolide  | Antimalarial activity by chaperon folding                                                | Talaromyces wortmannii        | Ding et al. (2010)                |
| *Chalara alabamensis*         | *Asterogyne martiana*                                                                     | *Tripterygium wilfordii*      |                                   |
| Sesquiterpenoids              |                                                                                          |                               |                                   |
| Chloropupukeananin            | Inhibited the HIV-1 replication in C8166 cells and also exhibited weak antibacterial activity | Pestalotiopsis fici           | Garcinia bracteata                 |
| *Periconia sp.*               |                                                                                          |                               | Liu et al. (2008a)                |
| Periconianone                 | Anti-inflammatory activity against lipopolysaccharide induced (LPS) NO production in mouse microglia B V2 cells | *Annona muricata*             |                                   |
| Pestalotiopsin                | Immunosuppressive agent                                                                   | Pestalotiopsis sp.            | *Taxus brevifolia*                |
| Diterpenoids                  |                                                                                          |                               | Pulici et al. (1996a)             |
| Guanacastepene                | Potent antibacterial activity against MRSA and vancomycin-resistant *Enterococcus faecalis* (VREF) through disrupting the cell membrane. | Unidentified fungus           | *Daphnopsis americana*            |
| *Trichoderma spp.*            |                                                                                          |                               | Brady et al. (2001)               |
| Harziandione                  | Antimicrobial activity against plant pathogens                                            | *Algae*                       | Miao et al. (2012)                |
| Sesterterpenoids              |                                                                                          |                               |                                   |
| Asperterpenoid, asperterpenols, and aspterpenacids | Acetylcholinesterase (AChE) inhibition and antibacterial activity                          | *Aspergillus spp.*            | Mangrove                         |
| *Brady et al.*                |                                                                                          |                               | Liu et al. (2016)                 |
and pyrones: pestalopyrone and hydroxypestalopyrone (endophytic to *Torreya taxifolia*) (Lee et al. 1995b), caryophyllene sesquiterpenes such as pestalotiopsins A and B (endophytic on *Torreya brevifolia*) (Pulici et al. 1996a), 2-alpha-hydroxydimeninol and humulane (Pulici et al. 1996b). These reports revealed that the same species but different strains associated with different plants can produce a variety of natural bioactive secondary metabolites. The ecological condition and the host plant together influence the variation in the production of secondary metabolites. One of the studies reported that antifungal jesterone and hydroxyjesterone were produced by the endophyte *Pestalotiopsis jester* obtained from the Sepic river area of Papua New Guinea (Hu et al. 2001). Another study reported that endophytic *Phomopsis* sp. produce phomopsichalasin, an antibacterial metabolite act against *Bacillus subtilis*, *Salmonella enteric* serovar *Gallinarum*, and *Staphylococcus aureus* (Horn et al. 1995). An antifungal compound, CR377, isolated from the endophyte *Fusarium* sp. associated with the plant *Selaginella pallescens*, exhibited remarkable activity against *Candida albicans*. A natural compound Colletotric acid produced by *Colletotrichum gloeosporioides*, associated with the plant *Artemisia mongolica*, showed antimicrobial action against several bacteria as well as a fungus, *Helminthsporium sativum*. Another *Colletotrichum* sp., associated with the plant *Artemisia annua*, produced artemisinin, an important antimalarial drug (Lu et al. 2000). Endophytic *Streptomyces* sp. strain NRRL 30562 from *Kennedia*
*nigriscans* produced wide-spectrum antibiotics called munumbicins (Castillo et al. 2002). These antibiotics have different biological activities based on their target organism, but generally, they exhibited antibacterial activity against *Bacillus anthracis* and multidrug-resistant *Mycobacterium tuberculosis*. Endophytic fungi isolated from *Ginkgo biloba* L. showed antimicrobial activity against gram-positive and gram-negative bacteria. *Xylaria* sp. YX-28, an endophyte isolated from *Ginkgo biloba* L., disclosed the presence of an antimicrobial compound 7-amino-4-methylcoumarin (Liu et al. 2008b). Another fungal species *Penicillium cataractum* SYPF 7131 from the plant produced antimicrobial compounds such as penicimenolidyru A, penicimenolidyru B, and rasfonin (Wu et al. 2018). Zhao et al. (2010) reported that *Pichia guilliermondii* Ppf9 isolated from *Polyphylla Yunnanensis* produced three steroids and one nordammarane triterpenoid, ergosta-5,7,22-trien-3β,5α,8α-epidioxyergosta-6,22-dien-3β-ol, and ergosta-7,22-dien3β,5α,6β-triol and helvolic acid, which exhibited antimicrobial activity against *Agrobacterium tumefaciens*, *Escherichia coli*, *Pseudomonas lachrymans*, *Bacillus subtilis*, *Xanthomonas vesicatoria*, *Ralstonia solanacearum*, *Staphylococcus aureus*, and *Staphylococcus haemolyticus*. Phaopongthai et al. (2013) reported that *Alternaria alternata* associated with *Terminalia chebula* produced a vast variety of antimicrobial compounds such as Altenusin, isoochracinic acid, altenuic acid, and 2,5-dimethyl-7-hydroxychromone. The compounds such as epicolactone and epicoccolides A and B reported from the fungus *Epicoccum* sp. CAFTBO isolated from *Theobroma cacao* exhibited antifungal activity against *Pythium ultimum* and *Rhizoctonia solani* (Talontsi et al. 2013). Chapla et al. (2014) demonstrated the new antimicrobial compound, 2-phenylethyl-1H-indol-3-yl-acetate, and seven known compounds such as uracil, cyclo-(S*-Pro-S*-Tyr), cyclo-(S*-Pro-S*-Val), 2-(2-aminophenyl)-acetic acid, 2-(4-hydroxyphenyl)acetic acid, 4-hydroxybenzamide, and 2-(2-hydroxyphenyl)-acetic acid, from the fungus *Colletotrichum gloeosporioides* present in the leaves of *Michelia champaca*. Huang et al. (2015) characterized five novel guaiane sesquiterpenes from the endophytic fungus *Xylaria* sp. YM 311647 isolated from *Azadirachta indica*. The compounds showed antimicrobial activity against fungal pathogens *Candida albicans*, *Aspergillus niger*, *Pyricularia oryzae*, *Fusarium avenaceum*, and *Hormodendrum compactum*. Silva et al. (2017) reported the antifungal activity of three new isoaigialones, along with aigialone from the fungus *Phaeoacremonium* sp. isolated from the leaves of *Senna spectabilis*. One of the studies reported that an endophytic fungus *Aspergillus clavatonanicus* strain MJ31 produced seven antibiotics such as miconazole, fluconazole, ampicillin, ketoconazole, streptomycin, rifampicin, and chloramphenicol, and several other volatile compounds (Mishra et al. 2017). *Penicillium commune*, *Penicillium canescens* and *Alternaria alternate* were isolated from *Olea europaea* L. reported producing six volatile compounds, where 3-methyl-1-butanol and phenylethyl alcohol ascribed as potent antimicrobial agents (Malhadas et al. 2017). *Seltsamia galinsogisoli*, an endophyte isolated from the plant *Galinsoga parviflora*, produced antimicrobial compounds Seltsamiayu and Galinsogisoliyu along with several other known secondary metabolites (Zhang et al. 2019). Endophytic *Penicillium skrjabinii* associated with the host plant *Pelargonium sidoides* DC. produced a...
potent antimicrobial agent dibutyl phthalate which inhibited *Staphylococcus aureus* and *Escherichia coli* at lower concentrations (Aboobaker et al. 2019). Fungal species belongs to the genus *Lecanicillium* isolated from *Sandwithia guyanensis* produced five stephensiolides compounds that demonstrated antibacterial activity against methicillin-resistant *Staphylococcus aureus* (MRSA) (Mai et al. 2020). Several endophytic actinomycetes were found to produce antimicrobial compounds such as actinoallolides belong to the class of macrolides (*Actinoallomurus fulvus* MK10-036), trehangelins which comprise of two trehalose molecules and an angelic acid (*Polymorphospora rubra* K07-0510), and spoxazomicins, pyochelin class of antibiotics (*Streptosporangium oxazolinicum* K07-0460) (Nakashima et al. 2013; Inahashi et al. 2011; Inahashi et al. 2015). An endophytic actinomycete strain BCC72023 derived from rice (*Oryza sativa* L.) produced three macrolide classes of bioactive compounds such as efomycins M, G, and oxohygrolidin and two polyethers such as abierixin and 29-O-methylabierixin. All of these compounds displayed antimalarial activity against the *Plasmodium falciparum*, K-1 strain, and different strains of bacteria such as *Mycobacterium tuberculosis*, *Bacillus cereus*, *Colletotrichum gloeosporioides*, and *Colletotrichum capsici* (Supong et al. 2016). Studies on potential antimicrobial compounds from endophytic actinomycetes are scarce and need to be addressed abundantly because of its vast diversity and the presence of several natural compounds (Matsumoto and Takahashi 2017).

Antiviral compounds were also reported from endophytic organisms; however, there had been limited reports on antiviral metabolites from endophytes. The endophytic fungus *Cytomaema* sp. was reported producing two antiviral compounds such as cytonic acids A and B. These compounds act against human cytomegalovirus by inhibiting proteases (Guo et al. 2000). Hinuloquinone is another active compound which inhibits human immunodeficiency virus type 1 protease (HIV-1), isolated from an endophytic fungus *Nodulisporium hinnuleum* associated with the leaves of *Quercus coccifera* (Singh et al. 2004). *Streptomyces tsusimaensis* an endophyte reported producing the compound valinomycin which acts as an antiviral compound against the corona virus. Another study reported that the endophyte *Xylaria* sp. produced a natural compound such as dihydroxynaphthol (glucopyranoside) which inhibits the Herpes virus (Pittayakhajonwut et al. 2005). Zhang et al. (2014b) reported that the endophytic fungus *Emericella* sp. isolated from *Aegiceras corniculatum* produced two isoindolone derivatives acted against influenza A (H1N1). An extensive literature survey showed that the potential studies on the discoveries of antiviral compounds from endophytes are rudimentary. The major constraint in antiviral compound finding is perhaps associated with the deficiency of proper screening methods.

### 5.4.2 Anticancer Activity of Endophytic Natural Compounds

One of the studies reported that the endophytic fungus, *Taxomyces andreanae*, from the plant *Taxus brevifolia* produced an anticancer compound, paclitaxel (Dong et al. 2014). It is a diterpenoid, exceedingly functionalized compound that prevents
tubulin molecules from depolymerization during cell division (Schiff and Horwitz 1980). Another report showed that the endophyte Pestalotiopsis microspora isolated from Taxus wallichiana produced paclitaxel (Strobel et al. 1996). Moreover, numerous other Pestalotiopsis microspora isolated from bald cypress was also reported to produce paclitaxel (Strobel et al. 1996). Another endophyte Pestalotiopsis guepini from Wollencia nobilis was also reported to produce paclitaxel (Strobel et al. 1997). Furthermore, fungal endophytes Periconia sp. and Seimatoantlerium nepalense were reported to produce paclitaxel (Li et al. 1998; Bashyal et al. 1999).

Torreyanic acid is another anticancer compound produced by the endophyte Pestalotiopsis microspora strain isolated from Taxus taxifolia. The compound induces apoptosis in cancer cell lines which are sensitive to protein kinase C agonists (Lee et al. 1996). Cytochalasins is a potent anticancer agent reported from endophytic genera such as Xylaria, Phoma, Hypoxylon, and Chalara. Around 20 species of fungi have been reported to produce the alkaloid compound, cytochalasins (Wagenaar et al. 2000). Entrophospora infrequens, an endophyte derived from Nothapodytes foetida, was reported to generate an effective antineoplastic agent camptothecin (Puri et al. 2005). Furthermore, analogs of camptothecin such as topotecan and irinotecan were isolated from Fusarium solani associated with the host plant Camptotheca acuminata, and the two compounds were successfully developed as clinically useful anticancer agents (Kusari et al. 2009b). Kang et al. (2014) also reported camptothecin from the endophytic fungi Alternaria alternata, Colletotrichum gloeosporioides, Fusarium nematophilum and Phomopsis vaccinia, all of them isolated from Cyanea acuminata.

A nonalkaloid lignin called podophyllotoxin was first discovered from Trametes hirsute with tremendous anticancer prospective (Puri et al. 2006). Several other fungal species were reported to produce podophyllotoxin and other related teralin lignin. Aspergillus fumigatus derived from Juniperus communis (Kusari et al. 2009a), Phialocephala fortinii from the host plant Podophyllum peltatum (Eyberger et al. 2006) and Fusarium oxysporum derived from the plant Juniperus recurva (Kour et al. 2008) are some of the examples of podophyllotoxin and its analog producing endophytic fungi. Another game changing compound vincristine was extracted from the endophyte Mycelia sterilia associated with the host plant Catharanthus roseus (Yang et al. 2004). Vincristine is mostly applied as a chemotherapeutic agent in nephroblastoma and acute lymphoblastic leukemia.

### 5.4.3 Endophyte Derived Antioxidant Agents

Pestalotiopsis microspora, an endophyte derived from Terminalia morobensis, reported to produce two antioxidant and antimicrobial compounds, pestacin and isopestacin. The antioxidant activity of isopestacin by scavenging hydroxyl and superoxide free radicals was because of its structural resemblance to the flavonoids (Harper et al. 2003). Pseudocercospora sp. ESL 02 derived from the host plant Elaeocarpus sylvestris produced two antioxidant compounds such as terreic acid and 6-methylsalicylic acid. The natural compounds from the endophyte also had...
remarkable activities reducing power and β-carotene bleaching activity (Prihantini and Tachibana 2017). Two chemical compounds such as benzeneethanol and 1,4-diaza-2,5-dioxo-3-isobutyl bicycle [4.3.0] nonane identified in GC/MS from the endophyte *Diaporthe schini* showed remarkable antioxidant activity and suggested for pharmacological use (da Rosa et al. 2020). Another compound cajaninstilbene acid is a potential antioxidant compound isolated from several fungi such as *Fusarium solani* ERP-07, *Fusarium oxysporum* ERP-10, and *Fusarium proliferatum* ERP-13 inhabiting in the host plant *Cajanus cajan* (L.) (Zhao et al. 2012). The investigation of the fungus *Eurotium cristatum* EN-220 collected from the marine alga *Sargassum thunbergii* produced several bioactive compounds such as isovariecolorin I, dehydroechinulin, rubrumazine B, neoechinulin B, neoechinulin C, didehydroechinulin, alkaloid E-7, echinulin, and variecolorin H, all of them revealed antioxidant activity (Zhao et al. 2012). The list of compounds from endophytes does not end here. The search for better antioxidant compounds has been increased recently because of the current demand for the treatment or combating of different diseases.

### 5.4.4 Antidiabetic and Immunosuppressant Compounds from Endophytes

Insulin mimicking nonpeptidial fungal compound L-783,281 was isolated from *Pseudomassaria* sp. from the rainforest of Democratic Republic of the Congo (Lenz 2000). Unlike insulin, the compound would not destroy the digestive system and could be administered orally. Orally administered L-783 significantly lowered the blood glucose levels (Lenz 2000). α-Glucosidase inhibitor, a potent antidiabetic agent, producing endophytic *Actinomycetes* sp. was isolated from *Caesalpinia sappan* (Irawan and Biologi 2009), and *Streptomyces* sp. have also reported to harbor a significant antidiabetic potential compounds (Pujiyanto et al. 2012). *Penicillium* sp. derived from *Tabebuia argentea* produced octadecanoics, a potent antidiabetic agent which inhibited all diabetic protein activity (Murugan et al. 2017). Another endophytic fungi, *Alternaria* sp., derived from *Salvadora persica* produced cetene and 1,2-benzenedicarboxylic acid which showed promising antidiabetic activity (Elgorban et al. 2019). These findings would lead to a new treatment for diabetes.

Immunosuppressants are agents that are commonly used in graft rejection problems as well as in the treatment of autoimmune diseases. One of the studies conducted in the endophytic *Fusarium subglutinans*, obtained from *Tripterygium wilfordii*, produces the compound subglutinol A and B. These compounds are noncytotoxic diterpene pyrones and equipotent in the mixed lymphocyte assay and thymocyte proliferation assays (Lee et al. 1995a). Another study revealed that the endophytic fungus *Tolypocladium inflatum* produced cyclosporine, a tremendously used immunosuppressant (Ramana Murthy et al. 1999). Curtachalasins is a potent immunosuppressive agent derived from the endophytic fungus *Xylaria* cf. *curta* isolated from rice. Lipopolysaccharide (LPS)-driven B lymphocyte cell proliferation
revealed that the compound Curtachalasins inhibited B-cell proliferation and selectively inhibited T-cell proliferation (Wang et al. 2019).

5.5 Conclusion

Without any question, endophytes continue as an eminent biodiversity and warehouse of new natural bioactive molecules with useful activities and give a base to novel drugs against untreatable diseases or conditions. The selection of endophyte does matter in terms of their bioactive molecule production. Ecological adaptations as well as challenging ecological niche encourage the endophyte as well as the host plant to produce a diverse array of natural compounds. New biotechnological advancements, metabolic technology, and advanced microbial culturing technology envisaged the isolation and identification of bioactive endophytes as well as their natural compound production. A better understanding of the mechanism of bioactive compounds production could give us to manipulate the organisms to produce an increased amount of natural bioactive compounds. However, studies in the area of endophyte bioactive metabolite production and their successful pharmacological applications need to be conducted. Finding new drugs from endophyte is undoubtedly dazzling.

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