Proceedings of the Pakistan Academy of Sciences: B
Life and Environmental Sciences 59(4): 1-13 (2022)

ISSN (Print): 2518-4261; ISSN (Online): 2518-427X
http://doi.org/10.53560/PPASB(59-4)780

Pakistan Academy of Sciences

Review Article

Endophytes: Potential Source of Bioactive Compounds of Pharmaceutical Importance

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Abstract: Microbes exists as mutualists, parasite, and symbiont or as pathogens in nature. In plant microbiota, plant immunity determines whether the interaction with microbes is friendly or hostile. Friendly interaction may have an eccentric way of mutual interrelations for a resource contribution. This interaction is called plant-endophyte mutualistic or symbiotic relation in which microorganisms (fungi, bacteria and actinomycetes) live within robust plant tissues. It has been discovered that almost all plant species investigated by various researchers harbor one or more endophytes. They benefit their host by producing various secondary metabolites that can be employed in agriculture and medicine. Endophytes are a treasure house of many novel bioactive compounds such as steroids, tannins, terpenoids, quinones, alkaloids, saponins and phenolic acids which makes them a potential candidate for anticancer, antibiotic, antioxidant, anti-inflammatory, antiviral, antidiabetic properties, etc. Endophytes continue to be the peculiar source of various potential drugs. This review intends to shed light on the function and potential applications of endophytes as a forthcoming source of medications for a range of illnesses/diseases as well as other potential medical uses.

Keywords: Endophytes, Antibiotics, Antimicrobial, Medicinal Plants, Secondary Metabolites, Pharmacology

1. INTRODUCTION

Phytomicrobiome associated with the different plant structures plays an essential role in which microorganisms in the microbiome provide different beneficial services to the plants causing without any immediate, overt and adverse effect on the host plant [1]. These plant growth-promoting endophytes act as a valuable agricultural resource as they form symbiotic associations with their host plant by penetrating internal tissues. The host plant provides protection and nutrients to the endophytes and these endophytes produce the bioactive compounds that add to the protection against herbivores and plant diseases, as well as boost resilience to a variety of stresses [2]. Endophytes, particularly endophytic fungi, are found to have a wide spectrum of bioactive compounds, and hence Owen and Hundley [3] referred to them as "the chemical synthesizer inside the plant". Various endophytic microbes have been identified and studied over the last 50 years, leading to the biological and chemical characterization of many natural products with distinctive structures and biological activity [4]. According to recent research, secondary metabolites produced by endophytes may be the primary source of protection against diseases [2]. Endophytes are gaining industrial and biotechnological relevance due to their potential to produce various bioactive compounds which act as antitumor agents, biocontrol agents, antimicrobial agents, immunosuppressants and release antiviral compounds, as well as the production of natural antibiotics, antioxidants, insecticidal and antidiabetic products [5].

Plants are being widely investigated for novel chemical entities that may exhibit diverse therapeutic properties and endophytes play a significant role in the search for compounds with potential applications in health and medicine [6]. Endophytes have produced a large number of

Received: September 2022; Accepted: December 2022
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bioactive substances that have been identified and characterized by many researchers like vincristine, taxol, podophyllotoxin, hypericin and many others given in the tables below. With an emphasis on endophytic bacteria and fungi, this study elucidates the endophytic bioactive compounds and their pharmacological applications.

2. AN OVERVIEW OF ENDOPHYTES

Endophyte was initially defined by De Bary [7] who stated that "any organism that resides inside plant tissues is referred to as an endophyte." However, the definition continues to evolve based on the findings of other researchers [8, 9]. Depending on the colonization's nature and their potential roles, plant associations with microbes can be characterized as mycorrhizal, pathogenic, epiphytic, saprotrophic, and endophytic [10]. Endophytes can penetrate the internal tissues of the plant. Endophytes like fungi, bacteria, eukaryotes, and archaea grow within plant tissues and are recognized to cause no harm to plants. Endophytes show symbiosis with the tissues of plants that are occasionally harmful. Wheat, rice, maize, mustard, chili, soybean, tomato, citrus, and sunflower are just a few of the plants that have been found to have endophytic microorganisms [11, 12].

They have grabbed the attention of many scientists due to their ability to promote plant growth and plant survival in stressful conditions [13]. Natural compounds produced by endophytes are beneficial in agriculture, medicine and in industries (Figure 1). The type of microbe that can be associated with a plant strongly relies on the composition of its root exudates. [14]. Endophytes utilize the root exudates as a source of energy which is essential for their association with host plants [15,16].

3. ENDOPHYTES: SOURCE OF POTENTIAL BIOACTIVE COMPOUNDS

At present, the entire world's population is tormented by deadly chronic diseases. The therapeutic potential and efficacy of antibiotics are being constrained by the rise in bacterial resistance to commercial antibiotics. Therefore, it is crucial to look for innovative, affordable, and non-toxic natural bioactive chemicals from endophytes for producing novel drugs with diverse mechanisms to fulfill people's needs. Endophytes have been mentioned in several publications as excellent sources of bioactive compounds and their beneficial role in the cosmetic and drug industries. Numerous bioactive compounds isolated from different endophytic fungi of medicinal plants are now used in both pharmaceutical and agricultural applications e.g. Paclitaxel is a well-known and highly functionalized tetracyclic diterpenoid bioactive compound was discovered from the fungus Taxomyces andreanae. It has proved to exhibit efficient activity against prostate, ovarian, breast, and lung cancers [17].

3.1 Antibiotics

Bioactive compounds that are active against pathogenic microbes at low concentrations are characterized as antibiotics [18]. Strobel and Daisy [19], summarized the antibiotics identified from endophytes, the majority of which were proven to

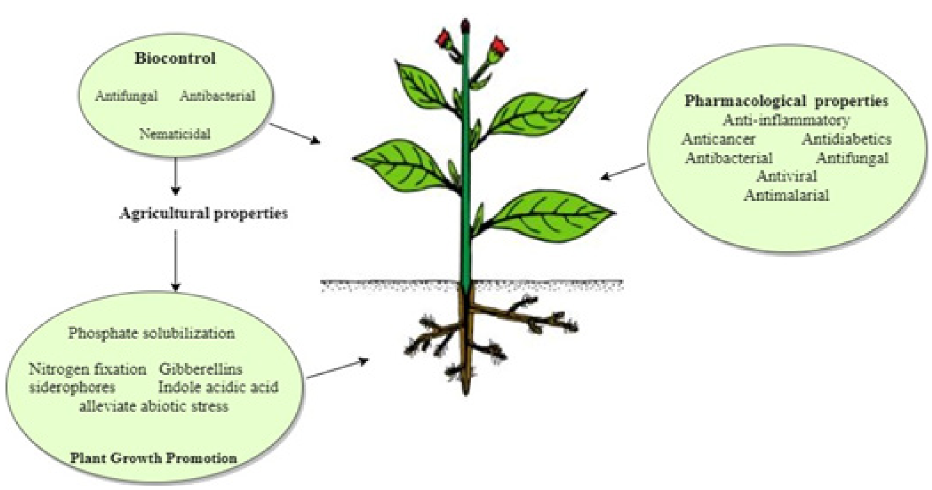

Fig. 1. Metabolites and functions of beneficial endophytes

be relevant. During the last 10 years, significant progress has been made and prior work has been evaluated and updated in Table 1.

3.2 Anticancer Compounds

Over six million new cases of cancer are reported each year, making it one of the most fatal diseases in the world. Many bioactive compounds from microbes, plants, and marine sources have been investigated as anticancer medicines; there is some indication that some endophytes produce natural compounds that can be used in treating different types of cancer [53]. Several secondary metabolites extracted from endophytes that have lately been studied for their anticancer effects are mentioned (Table 2).

3.3 Antioxidant Compounds

These are compounds that can shield cells from the damage caused by reactive oxygen species (ROSs),

Table 1. Antibiotics produced by endophytes.

Endophytes	Host Plant	Activity	Bioactive Compound	References
Endophytic Bacteria				
Bacillus subtilis	*Allanmandas cathartica* L.	Antifungal	Terpenoids	[20]
B. subtilis, B. licheniformis and B. pumilus	*Moringa peregrina* (Forssk.)	Antifungal and Antibacterial	-	[21]
B. subtilis	-	Antifungal	Phospholipids	[22]
Pseudomonas, Enterobacter, Staphylococcus, Lysinibacillus	*Combretum molle*	Antibacterial and Antifungal	-	[23]
B. subtilis	-	Antibacterial	Peptides	[24]
B. mojavensis, B. atrophaeus	*Glycyrrhiza uralensis* Fisch.ex DC.	Antifungal	Polyketides	[25]
B. thuringiensis	*Physalis alkekengi* L.	Antibacterial	-	[26]
Amycolatopsis tolypophora	*Stachys lavandulifolia* Vahl.	Antibacterial	-	[27]
Endophytic Fungi				
Acremonium zeae	*Zea mays* L.	Antifungal	Pyrrocidines A, B	[27]
***Nodulisporium* sp.**	*Juniperus cedre* L.	Antibacterial	Flavonoids	[28]
Phomopsis* sp. *Acremonium zeas* *Chaetomium globosum	*Ginko biloba* L. *Zea mays* L. *Garcinia dulcis* (Roxb.) Kurz	Antifungal and Antibacterial	Alkaloids	[29,30, 27]
***Cryptosporiopsis* sp. *Pezicula* sp.**	*Pinus sylvestris* L. *Fagus sylvatica* L.	Antifungal and Antibacterial	Peptides	[31, 32]
Chaetomium globosum	*Ginko biloba* L.	Antifungal	Azaphilone derivative	[30]
Pestalotiopsis mangiferae	*Magnifera indica* L.	Antibacterial	Phenols	[33]
***Aspergillus* sp.**	*Bauhinia guianensis* Aubl.	Antibacterial	Alkaloids	[34]
***Xylaria* sp.**	*Abies holophylia* Maxim.	Antifungal	-	[35]
***Phompsis* sp.**	*Aconitum carmichaelii Debeaux.*	Antifungal	Steroids	[36]
***Phoma* sp.**	*Cinnamomum* Schaeff.	Antibacterial and Antifungal	Polyketides	[37]

Endophytes	Host Plant	Activity	Bioactive Compound	References
***Phomopsis* sp. *Botryosphaeria* sp.**	*Gracinia* L.	Antifungal and Antibacterial	-	[38]
Geotrichum candidum	*Phyllanthus reticulatus* Poir.	Antifungal and antibacterial	-	[39]
Nigrospora sphaerica	*Indigofera suffruticosa* Mill.	Antibacterial	-	[40]
Endophytic Actinomycetes				
***Streptomyces sp.* DSM 1175**	*Alnus glutinosa* L.	Antibacterial	Quinones	[41]
Streptomyces sp.	*Grevillea pterdifolia* Knight.	Antibacterial	Peptides	[42]
Streptomyces noursei	-	Antifungal	Steroids	[43]
***Dactylosporangium* sp.**	*Cucubalus* L.	Antifungal	Tannins	[41]
***Streptomyces auereofaciens* CMUAc130**	*Zingiber officinale* Rosc.	Antifungal	Coumarins	[44]
Aeromicrobium poni	*Vochysia divergens* Pohl	Antibacterial	Alkaloids	[45]
Streptomyces sp.	*Aucuba japonica* Thunb.	Antibacterial	Terpenoids and terpenes	[46]
***Streptomyces* sp.**	*Boesenbergia rotunda* (L.) Mansf.	Antibacterial	Flavonoids	[47]
***Streptomyces* sp.**	-	Antibacterial	Peptides derivatives	[48]
Actinosynema pretiosum	*Maytenus serrata*	Antibacterial	polyketides	[49]
Verrucosispora maris	*Sonchus oleraceus* L.	Antibacterial	Peptides	[50]
***Streptomyces* sp.**	*Glycin max* (L.) Merr.	Antifungal	Alkaloids	[51]
Streptomyces remosus	-	Antifungal	Steroids	[52]

which are responsible for several pathological effects including cellular aging, carcinogenesis and DNA damage [87]. Cancer, atherosclerosis, rheumatoid arthritis, cardiovascular disease, ischemia/reperfusion injury, hypertension, neurological illnesses (Parkinson's and Alzheimer's diseases), diabetes mellitus, and aging have all been associated with ROS [88]. A novel compound sesquiterpene, 3,5-dihydroxy-2,5-dimethyltrideca-2,9,11-triene 4,8-dione has strong antioxidant activity isolated from *Acremonium* sp. [89]. A detailed list of antioxidant compounds isolated from endophytes and their uses against various diseases is presented in (Table 3).

3.4 Antiviral Compounds

The isolation of antiviral agents from endophytes is still new. The lack of antiviral screening mechanisms is the limiting factor in the endophyte synthesis of antiviral compounds. Some antiviral compounds isolated from endophytes are mentioned in (Table 4).

3.5 Antidiabetic Compounds

Nature has provided us with a plethora of natural compounds that can be used to treat various diseases. Glucose levels in the rats' blood had successfully reduced by endophytic fungi like *Aspergillus* sp. and *Phoma*. Kaur [108], also investigated endophytic fungi that could behave as alpha-glucosidase inhibitors such as *Fusarium* sp. and *Alternaria* sp. was also identified to secrete gancidinW (GW) that is active against α-glycosidase [109]. Extracts of endophytes isolated from the two most common medicinal plants Leucas ciliate and Rauwolfia

Table 2. Anticancer compounds isolated from endophytes

Endophytes	Anticancerous Compound	Activity	Cell lines used	References
Endophytic Fungi				
Fusarium oxysporum	Vincristine	Anticancer	-	[54]
***Acremonium* sp.**	Leucinostatins	Anticancer	-	[55]
Taxomyces andreanea	Paclitaxel	Anticancer	-	[56]
Lasidiplodia theobromae	Taxol	Anticancer	MCF-7	[57]
Cephalotheca faveolata	sclerotiorin	Anticancer	Colon cancer (HCT-116)	[58]
Enthrophospora infrequens	camptothecin	Anticancer	-	[59]
Trametes hirsute	Podophyllotoxin	Anticancer	-	[60]
Fusarium oxysporum	Podophyllotoxin	Anticancer	-	[61]
Aspergillus fumigatus	Cytotoxic alkaloids	Cytotoxicity	Leukemia cancer cells	[62]
***Garcinia* sp.**	Ethyl acetate extract	Antiproliferative and cytotoxicity	Vero cell lines	[63]
Penicillium sp.	Penicillenone	Anticancer	-	[64]
Colletotrichum gloesporiodes	Taxol	Cytotoxicity	Human cancer cell lines BT220, int407,H116 and HLK210	[65]
Mycellia strerilia	Vincristine	anticancer	-	[66]
Alternaria alternata	Ethyl Acetate extract	cytotoxicity	HeLa cells	[67]
C. gloesporiodes	Taxol	Anticancer	-	[68]
Phomopsis cassiae	3,12- dihydroxydalene 2,3,12- trihydroxycadalene	Antiproliferative	HeLa cervical cells	[69]
***Alternaria* sp.**	Xanalteric acid	Cytotoxicity	-	[70]
Fusarium solani	Camptothecin	Anticancer	-	[71]
***Alternaria* sp. *Colletotrichum* sp. *Chaetomium* sp.**	Ethyl acetate extract	Cytotoxicity	MCF-7 cells lines and HeLa	[72]
***Phoma* sp.**	*5- hydroxyramulosin*	Anticancer	-	[37]
***Penicillium* sp.**	*Arisugacin*	Anticancer	HeLa and K562	[73]
A. flavus	*Solamargine*	Cytotoxicity	-	[74]
Emericella variecolor	*Tajixanthone hydrate*	Anticancer	-	[75]
***Pestalotiopsis* sp.**	Pestalotiopsone A,B,C,D,E,F	Anticancer	L5178Y	[76]
***Guignardia* sp. *Halorosellinia* sp.**	Anthracene-9,10-dione 1-hydroxy-3-methyl	Anticancer	KB KBv200	[77]
***Fusarium* sp.**	5-O-methyl-2′-methoxy-3′-methylalpinumisoflavone	Anticancer	HEp2 HepG2	[78]
***Paecilomyces* sp**	Paeciloxocins A Paeciloxocins B	Anticancer	HepG2	[79]

Endophytes	Anticancerous Compound	Activity	Cell lines used	References
Endophytic Bacteria				
***Pantoea* sp.**	Ethyl acetate	Anticancer	A549 LUNG CARCINOMA and UMG87 glioblastoma	[80]
Acinetobacter guillouiae	Ethyl acetate extract	Anticancer	A549 lung carcinoma cells	[81]
Bacillus subtilis	Camptothecine	Anticancer	-	[82]
Endophytic Actinomycetes				
***Streptomyces laceyi* MS53**	6-alkalysalicilic acids, salaceyins Aand B	Anticancer	-	[41]
Actinosynnema pretiosum	Ansamitocin	Antitumor	-	[49]
Streptomyces thermoviolaceus	Anicemycin	Anticancer	-	[83]
***Streptomyces* sp. SUC1**	Lansai A-D	Antitumor	-	[84]
***Streptomyces* sp. CS**	Naphtomycin	Antitumor	-	[85]
***Micromonospora lupine Lupac* 08**	Lupinacidin C	Antitumor	Murine colon	[86]

Table 3. Antioxidant compounds from endophytes.

Endophytes	Host Plant	Bioactive Compounds	Class of Compounds	References
Endophytic Bacteria				
Methylobecterium radiotolerans	*Combret eryhrophyllum* (Bruch.) Sond.	Chloroform EtOAc	Alkaloids, flavonoids	[90]
Pseudomonas hibiscicola, Micrococcus caseolyticus, Enterobacter ludwigi	*Aloe vera* (L.) Burm.f.	EtOAc	Flavonoids Alkaloids	[91]
***Pseudocercospora* sp.**	*Elaeocarpus Sylvestris* (Lour) Poir.	Terric acid and 6-methylsalicyclic acid	-	[92]
***Enterobactor* sp. EC3**	*Carica papaya* L.	Gallic acid	Phenolic compounds	[93]
Lactobacillus sp.	*Adhathoda beddomei*	EtOAc	Phenolic compounds	[94]
Endophytic Fungi				
***Phomopsis loropetali* AcapF3**	*Tapernaemontana divaricate* L. *Rauvolfia verticillate* (Lour.) Baill.	-	Phenolic compounds	[79]
***Phyllosticta* sp.**	*Guazuma tomentosa*	EtOH	phenol	[95]
Phoma* sp., *Colletotrichum spiralis	-	MeOH	phenol	[96]
Alternaria alternata Aspergillus flavus, A. niger	*Lannea coromendalica*	EtOAc	Phenolic compound	[97]
Aspergillus minisclerotigens* AKF1 and *Aspergillus oryzae	*Mangifera casturi*	4H-Pyran-4-one and dihydropyran	-	[98]
***Aspergillus* sp.**	*Euphorbia prostrate* Aiton.	Gallic acid	Phenol	[99]
Chaetomium globosum	*Adiantum capillus* L.	EtOAc	Phenol	[100]

Endophytes	Host Plant	Bioactive Compounds	Class of Compounds	References
Endophytic Actinomycetes				
***Streptomyces aureofaciens* CMUAc130**	*Zingiber officinale* Rosc.	5,7- dimethyl -4- p-methoxyl phenyl coumarin	Coumarins (alpha benzopyrones)	[44]
***Streptomyces* sp. MS1/7**	-	2- Allyloxyphenol	phenol	[101]
***Micromonospora* sp. PC1052**	*Puereria candoliei*	S-adenosyl-nacetylhomocysteine	peptides	[102]

Table 4. Antiviral compounds from endophytes.

Endophyte	Host Plant	Antiviral Compound	Reference
Pestalotiopsis theae	Unidentified tree on Jianfeng Mountain, China	Pestalotheol C	[103]
***Paecilomyces* sp.**	*Taxus mairei*	Brefeldin A	[104]
Fungal isolate	*Quercus coccifera* L.	Hinnuliquinone,	[105]
***Cytonaema* sp.**	*Quercus* L.	Cytonic acids A and B	[106]
***Pullularia* sp. BCC 8613**	Unidentified tree	Pullularin A	[107]

densiflora were evaluated by Akshatha *et al*. [110] for their anti-diabetic potential.

3.6 Antiarthritis and Anti-Inflammatory Compounds

Rheumatoid arthritis (RA) is a systemic, autoimmune and inflammatory disease that causes swelling, discomfort, bone and cartilage degradation, and can eventually cause permanent disability. Surprisingly, the disease's actual causal agent remains unknown. Many researchers are currently hunting for additional therapeutic compounds from microorganisms because synthetic medications are currently quite expensive and have a lot of drawbacks [111]. Methanolic extract of endophytic fungi Talaromyces wortmannii from *Aloe vera* produced compounds with anti-inflammatory properties [112]. Endophytic fungi *Lepidosphaeria* sp. also has anti-inflammatory action, suggesting that inflammatory diseases such as rheumatoid arthritis can be treated [113].

4. CONCLUSION AND FUTURE PERSPECTIVE

The present review summarized the facts of endophytes-mediated bioactive compounds that are symbiotically associated with different plant species and are an interesting source of novel therapeutic compounds. Different plant species have different endophytes that serve as a vital source of significant natural compounds that are beneficial in agriculture, medicine and in industries. These bioactive compounds are produced under particular-environmental conditions, stressful conditions, nutrient availability, or during a particular developmental stage. They possess different therapeutic activities such as antibacterial, antioxidant, antidiabetic anti-inflammatory, anticancer, antiviral, and antimalarial, etc. Therefore, there is a further need to isolate endophytes and their secondary metabolites from medicinal plants to discover novel compounds for therapeutic/pharmacological purposes. Towards this aim, further insights into the origin of endophytic genes and dynamic endophyte-host plant interactions would be of utmost importance.

5. CONFLICT OF INTEREST

The authors declare no conflict of interest.

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